

# **Oscillatory activity in the human motor system**

**By**

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## **Abstract**

The human motor system is characterised by fast oscillatory neural activity at around 20 cycles per second. This so-called beta rhythm is commonly observed in the primary motor cortex and is transmitted via the spinal cord to muscle. The functional significance of this cortico-muscular coherence is uncertain.

Recent theories of the pathophysiology of Parkinson's disease have lead to the idea that the exaggerated expression of this oscillatory activity may in some way contribute to the symptoms of slowed movements (bradykinesia) and rigidity. In this thesis I provide evidence to argue that these oscillations may produce a transient impairment in the ability of healthy humans to produce effective ballistic speed associated with voluntary movements. Using a simple reaction time task in which the timing of movements was biased to coincide with transient increases in beta oscillatory activity, the ballistic acceleration of the movement could be impaired. Direct recording of local field potentials (ECOG) from the sensorimotor cortex in two patients during a similar reaction time task further confirmed that cortical beta activity was associated with a state of impaired ballistic motor performance. The properties of this neural state are further explored using a variety of neurophysiological techniques. In particular, beta oscillations were found to be associated with a state of enhanced responsiveness to sensory inputs relevant to motor control. Transcortical reflexes and the cortical components of the somatosensory evoked potential (SEP) were shown to be enhanced when preceded by periods of oscillatory activity.

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## Abbreviations used

<b>AD</b>	Analogue to digital	<b>ERS</b>	Event related
<b>ADM</b>	Adductor digiti minimi		synchronization.
<b>AMPA</b>	$\alpha$ -amino-5-hydroxy-3-methyl-4-isoxazole propionic acid	<b>FDI</b>	First dorsal interosseous
		<b>GABA</b>	Gamma aminobutyric acid
<b>AMT</b>	Active motor threshold	<b>HFS</b>	High frequency
<b>CL</b>	Confidence limits		stimulation
<b>CM</b>	Corticomotoneuronal	<b>IPSP</b>	Inhibitory postsynaptic potential
<b>CNS</b>	Central nervous system		
<b>CWT</b>	Continuous wavelet transform	<b>ISI</b>	Interspike interval
		<b>LED</b>	Light emitting diode
<b>DBS</b>	Deep brain stimulation	<b>LFP</b>	Local field potential
<b>DTF</b>	Discrete Fourier transform	<b>M1</b>	Primary motor cortex
		<b>MEG</b>	Magnetoencephalography
<b>ECOG</b>	Electrocorticography	<b>MEP</b>	Motor evoked potential
<b>EEG</b>	Electroencephalography	<b>MPTP</b>	1-methy 4-phenyl 1,2,3,6-tetrahydropyridine
<b>EI</b>	Extensor indicis		
<b>EMG</b>	Electromyography	<b>MRI</b>	Magnetic resonance imaging
<b>EPSP</b>	Excitatory postsynaptic potential		

<b>MUAP</b>	Multiunit action potential	<b>STA</b>	Spike triggered average
<b>MVC</b>	Maximal voluntary contraction	<b>TC</b>	Triggered cue
<b>PA</b>	Peak acceleration	<b>TMS</b>	Transcranial magnetic stimulation
<b>PCF</b>	Peak correlation frequency	<b>TS</b>	Triggered stretch
<b>PD</b>	Parkinson's disease		
<b>PSF</b>	Post spike facilitation		
<b>PTF</b>	Peak trigger frequency		
<b>RC</b>	Random cue		
<b>REM</b>	Rapid eye movement		
<b>RS</b>	Random stretch		
<b>RSE</b>	Residual squared error		
<b>RT</b>	Reaction time		
<b>S1</b>	Primary somatosensory cortex		
<b>SD</b>	Standard deviation		
<b>SEM</b>	Standard error of the mean		
<b>SEP</b>	Somatosensory evoked potential		
<b>SNR</b>	Signal to noise ratio		



# Chapter 1: Introduction

An obvious example of rhythmic motor action is walking. More difficult to appreciate subjectively is the fact that the voluntary actions that characterize human hand function are also discontinuous – consisting of rhythmic (oscillatory) neural discharges. The principle difference being that the oscillations that characterise hand functions such as precision grip are of a magnitude faster, typically around 10-40 per second, and are not visible to the eye under normal circumstances. Recent work in cultured brain slices have suggested that in the same way that the gross oscillatory behavior that characterizes walking is reflected in the activity of neurons recorded in the CNS (so-called central pattern generators), single neurons and networks of neurons, are capable of producing oscillations at frequencies consistent with those seen during motor action in the hand. It seems therefore that oscillations are a ubiquitous characteristic of motor behavior which may be expressed at the lowest level of nervous system organization – within single neurons themselves. Whereas the importance of a centrally oscillating network for the generation of a motor output to the lower limbs during walking seems fairly obvious, what benefit, if any, should fast oscillatory activity in hand muscles provide to motor behavior? The central topic that concerns this thesis is therefore the characterization of the properties of these oscillations in the context of human motor control of the hand. This introduction is aimed at providing a summary of the understanding to date of the organization of the motor control of the upper limb in the human and monkey, and a systematic review of the literature concerning oscillatory activity in the brain.

## 1.1 Motor Cortex

The primary motor cortex, M1, (or broadmann area 4) consists of a single gyrus that runs from the longitudinal fissure in the midline to the lateral cerebral fissure, bounded anteriorly by the precentral sulcus and posteriorly by the central sulcus. The realisation that this region of the brain has evolved to generate the actions that characterise our behaviour has been a process spanning over 100 years. Although the concept of localisation of function in the brain can be attributed mainly to the work of Jackson and Broca, the idea that the precentral gyrus contains a “motor map”, is associated mostly with the work of Sherrington in the monkey. The precentral homunculus of Penfield was the final in a series of observations that confirmed the motor cortex as the seat of action in the human brain. In this introductory chapter I will describe the specific cellular structure of M1, before considering the mechanisms by which these cells, when acting as a whole, contribute to the motor output.

### *Microscopic features of M1*

Microscopically the principle difference between M1 and other neocortical areas is the lack of any obvious layer IV. Of the cellular constituents that make up layers I-VI pyramidal neurons contribute 73% to the total with non-pyramidal contributing to the remainder (Porter and Lemon, 1993). The various different sizes of pyramidal neurons reside predominantly in layers III and V. These neurons use glutamate as their principle neurotransmitter. In contrast, non-pyramidal neurons can be found throughout all layers of the cortex. These cells are thought to be large, small and nested basket cells (or fast

spiking interneurons) whose synapses release the inhibitory transmitter GABA onto pyramidal cell soma or proximal dendrites (Houser et. al., 1983, Hendry et. al., 1983); chandelier cells, which synapse axonally; and the excitatory spiny stellate cells to name the most common classes (Markram et. al., 2004).

Intracortical connectivity is extensive between pairs of layer V pyramidal neurons, presumably through axonal collaterals, and has been observed functionally in the form of significant cross-correlations between pairs of neurons (Fetz and Finocchio, 1975). A further source of intracortical connectivity is from the layer III pyramidal neurons. Since the pyramidal neurons are arranged in groups forming radial columns through the layers, these sources of connectivity may provide a basis for the flexible re-organisation of relationships between pyramidal neurons projecting to different muscles or brain regions.

Input into the cells of M1 consists mainly of cortico-cortical fibres which project to both pyramidal and non-pyramidal neurons across all layers. Excitatory thalamo-cortical projections are found mostly in layer III and to a lesser extent to layer V. The connectivity of inhibitory interneurons is less well studied in the primate since these are technically difficult to identify. However, *in vitro* studies in rat motor cortex suggest a strong excitatory input from pyramidal neurons which are often reciprocally connected (Angulo et. al , 2003).

Approximately 20% of layer V neurons send axons that descend through the brainstem to form the cortico-spinal tract. The remaining fibres pass directly to the cerebellar or

reticular nuclei or to the basal ganglia. Finally, cortico-thalamic fibres arise from layer VI and pass back to the thalamic nuclei, completing a cortico-thalamo-cortical loop.

### *Functional organisation of M1 – output*

From the above description of intra-cortical connectivity in M1 it is perhaps unsurprising that considerable overlap exists between muscle representations. Although some convergence could be accounted for by common input at a spinal level, intra-cortical microstimulation in the primate often evokes identical movements from multiple, distributed sites (Kwan et. al ,1978; Huntley and Jones, 1991). Furthermore, Lemon et. al (1986) demonstrated with the use of spike triggered averages, that pyramidal neurons projecting to intrinsic muscles of the hand were from overlapping regions of the cortex. These studies confirmed the idea that although there was somatotopy in M1 on a gross scale, no simple 1-to-1 output relationship existed between pyramidal neurons and the lower motoneuron. If the spatial connectivity of neurons in M1 naturally biases the recruitment of multiple muscle representations, then how is it possible for humans to make the precise, fractionated movements that we are so reliant upon? Although part of the answer to this question probably lies in the large proportion of cortico-motoneuronal (CM) cells that characterise the human cortico-spinal tract, the role of cortical inhibitory connectivity in shaping the spatial properties of the motor output is well recognised (Jacobs and Donoghue, 1991). It is important therefore to view the intrinsic connectivity and its relationship to the functional organisation of M1's output as being amenable to both short and long term dynamic changes.

### *Functional organisation of M1 – input*

Pyramidal neurons in M1 respond to passive displacement of the limb. These responses are characterised by their strict spatial localisation (Lemon and Porter, 1976) and rapid onset (16-24ms). Studies in the non-human primate suggest that two sources of muscle spindle input may explain these “afferent input zones”. Firstly, indirect cortico-cortical projections from primary somatosensory cortex area 3a, the principle recipient of proprioceptive fibres (Asanuma and Arissian, 1984). Secondly, direct thalamocortical fibres synapse on layer III/V pyramidal neurons (Herman et al., 1985). The functional significance of this input will be discussed further in a later introductory chapter concerning the transcortical stretch reflex.

### *Responses of single neurons in M1 associated with movement*

In the classical experiments of Evarts (Evarts, 1968, 1972 and 1978), precentral neurons typically responded 60ms before the onset of movement, with some firing as early as 140ms. The onset of firing in a single neuron was also shown to correlate with the time of movement, suggesting a causal relationship between M1 firing and movement initiation. The ramping up of firing in these neurons suggested that a single spike was not sufficient for motoneuron depolarisation since EMG activity could only be attributable to periods of a high probability of neuronal firing. These experiments and subsequent investigations suggested that motor unit activation requires the spatial and temporal summation of EPSP's at the spinal level. The temporal structure of the burst of spikes prior to

movement was shown to significantly effect the properties of motor unit recruitment. Notably, inter-spike intervals of between 40 and 70 ms produced strong facilitation in comparison to intervals between 10 and 40 ms which were less effective. Lemon and Mantel (1989) suggested that such temporal properties may be of particular importance in the fine control of distal muscles. A further characteristic of the neural response associated with movement is the variability in the onset of responses in individual neurons even within the same muscle (Cheney and Fetz, 1980). The scatter of recruitment times leads to the impression of a highly variable temporal representation of movement across individual M1 neurons.

The relationship between neuronal firing in M1 and its relationship to force has been well studied in the non-human primate. Evarts demonstrated that M1 neurons increased their firing when increased load was applied to the limb without causing displacement (Evarts, 1968). M1 neurons show graded changes in firing rate over a small range of forces (Evarts et. al., 1983) , supporting further the suggestion that M1 is particularly important in the early recruitment of motoneurons that are involved in precise fine movements. Furthermore, some neurons may preferentially code force, acceleration (Smith et al. 1975) or both.

#### *Set related properties of M1 neurons.*

An important development in the understanding of the functional organisation of M1 was made by Cheney and Fetz (1980). Using a ramp and hold task CM cells could be

classified according to the pattern of firing response during the task. The majority of neurons (59%) showed a phasic increase in firing followed by a maintained tonic level of firing at a lower rate. In contrast, 28% of neurons displayed a tonic firing pattern which they maintained throughout the task. More recently, the concept of set specificity in M1 has been revisited by Kurtzer et. al (2005). These authors recorded the responses of neurons in M1 when mechanical load was applied to the limbs. By comparing the responses to load applied during movement to those applied during a postural hold the authors observed tuning properties suggestive of two distinct populations of neurons in M1.

#### *Population encoding in M1*

Since a single pyramidal neuron cannot produce movement by itself and seemingly possesses the capacity to act upon several muscles at one time, it seems likely that cooperativity between pyramidal neurons exists. Georgopoulos and co-workers demonstrated that single neurons in M1 had a preferred directional tuning which was often shared with other neurons (Georgopoulos et. al, 1982). The firing patterns of these neural ensembles have been shown to predict the direction of a movement better than firing patterns of single neurons. Furthermore, the neurons recorded in these experiments were shown to be specific in their directional tuning, no tuning to movement amplitude was observed. Spike synchronisation between pyramidal neurons is increased between pairs of neurons with a shared muscle field, suggesting that synchronisation may be important for the spatial organisation of neurons in M1 (Jackson et. al., 2003). Recently,

Rickert et. al (2005) have demonstrated encoding of movement direction by fast (>30Hz) oscillations in M1 suggesting that this manifestation of population activity may be specific to this set of neurons.

## **1.2 The corticospinal tract and motor unit.**

Many different regions of the brain send projections to the spinal cord to act upon the peripheral musculature. By far the most important for voluntary movement is the corticospinal tract. The cell bodies of the neurons that form the corticospinal tract originate from layer V of the pre and post-central gyri. These areas contribute 60 and 40% respectively to over 1 million neurons. The axons of these neurons descend through the internal capsule, into the brainstem where they cross over to terminate on the neurons of the spinal cord. Approximately 2 % of these neurons are fast conducting but the majority are slow conducting. Corticospinal neurons can make direct monosynaptic connections with the lower motoneuron or oligosynaptic terminations on inhibitory interneurons,  $\gamma$  motoneurons or, in the case of the post central projections, onto afferent neurons in the spinal grey matter (Rothwell, 1983).

### *Functional properties of cortico-spinal – motoneuronal interactions*

The most extensively studied corticospinal projection is that of the Cortico-Motoneuronal cells (CM). The connections formed by these corticospinal neurons are monosynaptic and are made most often by the fast conducting fibres, although slow conducting fibres also contribute to the CM system. The importance of these cells in voluntary movement is



reflected in their propensity to innervate the motoneurons of the hand muscles, suggesting a central role in the co-ordination of complex hand movements.

CM cells are identified by the process of averaging the rectified EMG to the timing of the recorded neurons spikes. This analytical technique is known as spike triggered averaging (STA). CM cells are identified by their significant post spike facilitation (PSF) reflected in the EMG averaged to the spike times. Using this technique, the functional pattern of CM cell projection onto the lower motoneuron has been studied extensively. One definitive conclusion of these studies is the existence of extensive branching of single CM cells onto several lower motoneurons. Fetz and Cheney (1980) found an average of 3 muscles showed significant PSF by a single CM cell. Lemon and Mantel (1989) argued for an average of 7. An important feature of this divergence was that CM cells tended to innervate groups of agonists or antagonists but rarely both. Functional synergies between prime movers (eg thumb adductor and FDI ) were frequently associated with shared CM innervation demonstrated by PSF (Buys et. al. 1986). Divergence was also dependant upon the extent of fractionation required in the limb. Upper limb muscles received the most divergent input, muscles in the thumb being innervated by a single CM cell.

Indirect evidence for CM cell divergence in the human has been provided by a series of patient studies which examined the extent of short-term synchrony between pairs of motor-units. This index of shared mono-synaptic input is reflected as a sharp peak in the spike cross-correlogram between pairs of single motor-units. Datta et. al (1991) demonstrated that this was absent in stroke patients. Synchrony was also present in the

completely deafferented patient studied by Baker et. al. (1988), suggesting that common input from muscle spindles could not account for the cross-correlogram peak. Finally, Farmer et. al (1990) studied a patient with Klippel – Feil syndrome in whom bilateral spinal innervation was present. In this patient synchrony was present between motor units from muscles on both sides. This is never observed in normal subjects.

In all, dimensionality reduction may be the function of divergence. A single 1-1 relationship between the upper and lower motoneurons would provide a highly refined system. The potential number of combinations would, however, create a brain with unmanageable complexity. Therefore divergence may have been an evolutionary compromise between the accuracy of the motor control required for the animal's behaviour and the number of neurons that were available to the brain for controlling the peripheral musculature (Porter and Lemon, 1993).

Since the major theme of this thesis is the role of oscillatory synchrony in corticospinal function, is there any evidence to suggest that synchronous corticospinal input increases the probability of motoneuron discharge? Lemon and Mantel recorded from primate CM cells and analysed the PSF of the motoneuron pool after sorting the spikes according to their interspike interval. Short ISI's of <10 ms produced strong PSF which was consistent with temporal facilitation. Interestingly, ISI's of between 40 and 70ms produced unexpectedly large PSF when the low level of EMG associated with this firing rate was taken into account. This ISI is centred within the beta oscillation band-width (13-35 Hz) these oscillations are thought to be generated in M1 (see later). This may suggest that this

frequency of input may be a biophysically optimal way of driving the lower motoneuron pool at low levels of contraction (Baker et. al. 1999). It should be noted however that in this study the mean ISI was 20 ms and no obvious peaks at 10 or 50ms were present. The fact that most of the neurons were firing at a rate suboptimal for PSF leaves open the question as to whether temporal facilitation makes an important contribution to motoneuron recruitment. Further caution in the interpretation of these results is also required in light of more recent knowledge of the oscillatory properties of M1. A simple explanation for the unexpectedly large PSF would be that the intrinsic property of M1 neurons to synchronise at 20Hz contributed to this non-linearity. Therefore ISI's at 50ms may be associated with large PSF not because this represents a supra-optimal ISI for lower motoneuron facilitation, but is rather an ISI associated with increased probability of cortical pyramidal neuron synchronisation.

### *Functional properties of the spinal chord*

From the above discussion it would seem that the cortex provides much of the “code” required to produce a voluntary movement and, at first glance, the spinal chord may appear subservient to its cortical master. Evidence from intraspinal microstimulation in frogs (Giszter et al., 1993) and cats (Lemay and Grill, 2004) would suggest that the spinal chord plays a far more active role in the shaping of the final movement outcome. Giszter stimulated frog spinal chord and observed responses in the limbs that were remarkable similar to those seen during natural behaviour. Furthermore, these so called force fields could be simulateously combined by dual simulation to produce a linear superimposition

of the individual force field vectors (Mussa-Ivaldi et. al. 1994). Thus from the potential combination of motor primitives stored within the intraspinal neuronal networks, multiple movement representations could be produced.

Futhermore, it would seem that the preparatory activity observed in spinal interneurons, would place the spinal chord within a distributed network of serial processors, including neocortical and basal ganglia structures, in the initiation of movement (Prut and Fetz, 1999). The spinal chord therefore can not be viewed as a simple output relay for the corticospinal tract neurons to communicate with muscle.

#### *Functional properties of the motor unit.*

Sherrington and Leyton coined the term “motor unit” to describe the quantal element that makes up all striated muscle in the human body. The motor unit consists simply of the motoneuron, the branches which innervate the muscle fibers and the muscle fibers themselves. Although the number, size and type of the muscle fibers can vary within and between the motor units of different muscles, the basic physiological properties are fairly universal. Typically, the function of the muscle dictates the relative proportions of either fast (fatigue sensitive) or slow (fatigue resistant) muscle fibers. Soleus contains predominantly slow fibers whereas gastrocnemius contains mainly fast, reflecting the postural and ballistic functions of these muscles respectively. The type of fiber dictates the size and corresponding conduction velocity of the motoneuron. Fast fibers are

innervated by large axon motoneurons with fast conduction times whereas slow fibers receive input from small diameter, slower conducting motoneurons.

The input resistance of the motoneuron determines the amount of depolarisation required to bring the neuron to threshold. Large axon fibres have lower input resistance than small fibres and are therefore recruited later than the latter. Furthermore, Eccles (1957) demonstrated that the EPSP was larger in motoneurons projecting to slow twitch fibers than the EPSP produced in large motoneurons. These differences result in the preferential recruitment of slow twitch fibres before fast twitch. This schema seems well adapted for generating tonic contractions of varying levels of strength. During low level contraction, small fatigue resistant units with low threshold are initially recruited. In order to generate a large muscle force further depolarizing current is required to recruit the large diameter motoneurons fibers which produce the final burst of fused muscle fiber activity associated with strong muscular contraction.

If the slow twitch fibers are recruited first, then how is it possible to generate a ballistic movement? The ability to generate rapid, synchronized fusion of the motor fibers resides in the firing properties of large axon motoneurons. In contrast to the small axon motoneurons, which fire tonically at around 10Hz, large axon motoneurons respond to a depolarizing current with a rapid burst of firing before accommodation to a slower firing rate (Granit et. al, 1963a, Granit et. al., 1963b, Kernell et.al., 1965). These differences in firing properties can be related to differences in the after-hyperpolarisation that is observed following the action potentials in these neurons. In small motoneurons the after-

hyperpolarisation is relatively prolonged whereas in large fibers this is shorter, permitting a more rapid recovery and hence higher firing rate. Common to both types of neuron is the progressive summation of the after-hyperpolarisation after successive spikes. This property makes motoneurons less sensitive to depolarizing input after the initial depolarizing stimulus has elicited several spikes. In other words, a motoneuron is more likely to produce a rapid change in firing rate if it has not been firing prior to the depolarizing stimulus. A second important property that allows recruitment of the fast motoneurons into ballistic movements is that the force threshold of these motoneurons is dependant upon the speed of the movement. Desmedt and Godaux (1977) recorded both small and large motor units from the FDI and compared the force threshold for unit recruitment during a slow finger movement to the force threshold during a ballistic movement. Although the recruitment order was always from slow to fast, the force threshold for the same large motor unit was three times smaller when a ballistic movement was produced compared to a slow finger movement. Interestingly, by stimulating cutaneous receptors in the first digit, the recruitment threshold for small motor units can be lowered while raising the threshold for large motor units recruitment (Garnett and Stephens, 1981). This may be one reason for the pre-synaptic spinal inhibition of cutaneous input observed prior to movement (Seki et. al., 2004).

### **1.3 Monosynaptic and transcortical stretch reflexes**

The muscle spindle is the sensory organ of muscle. It is structurally differentiated for the principle function of responding to stretch of the muscle bulk. On one hand this

contributes to the perception of movement through projections to the post-central gyrus, on the other, it may be critical to the optimal recruitment of muscle during movement. Anatomically, the spindle lies within the muscle belly surrounded by a thin membrane which divides the muscle into intrafusal (ie muscle spindle) and extrafusal fibers. The intrafusal fibers can be divided into two subtypes, which differ in the properties of their response to stretch. Dynamic bag fibers respond with a rapid and increasing firing rate during the dynamic phase of a stretch. These responses are relayed to the spinal cord via group Ia afferents which are the largest and fastest muscle spindle afferents. In contrast, the static bag fibers are innervated by group II afferents which fire tonically throughout the stretch (Matthews, 1964). The sensitivity of these fibers to stretch is determined by the degree of  $\gamma$ - motoneuron drive to the spindle in most muscles, with the intrinsic muscles of the hand being innervated by  $\beta$  motoneuron drive. These fusimotor neurons are in turn innervated by descending corticospinal input from M1 (Lemon and Porter, 1993). Fusimotor neurons are thought to maintain the optimal length tension relationship in the spindle fibers so that they respond rapidly to the smallest degree of stretch.

If the tendon of a muscle is tapped with a tendon hammer a short latency reflex response is generated in the muscle (about 20ms in the upper, 30ms in the lower limb). If the muscle is active at the time of the stretching stimulus the first response is followed by a second at approximately 50-80ms. A third can also be seen, but this is of a latency consistent with the subjects voluntary response to the stimulus. These responses are respectively known as the short and long latency stretch reflexes (M1, M2 and M3) and are the subject of the next introductory sub-chapter.

*What is the function of the short latency stretch reflex?*

The short latency reflex was found to be monosynaptic by Renshaw in the 1940s. Conduction velocity studies provided further evidence to suggest that this response was principally generated by  $\alpha$  motoneurons in response to Ia afferent input. In contrast, the origin of the long latency response is thought to be a polysynaptic pathway with a central component. The evidence for this will be treated separately below. The physiological functions of these reflexes are unknown. However, several theories have been proposed. Merton proposed one of the first theories of the mono-synaptic reflex function in 1956 (Hammond, Merton and Sutton, 1956). The so-called servo-control theory proposed that the movement was initiated by driving the  $\gamma$ -motoneurons prior to movement. This would increase the stretch in the muscle which would subsequently recruit the  $\alpha$ -motoneuron via the mono-synaptic pathway. Although this was disproved, since  $\gamma$ -motoneurons fire during but not before movement (Vallbo, 1970), the idea of a positive feedback loop between these two different types of motoneuron became important in later equilibrium point control theories of movement.

An influential basis for this theory came from the experiments of Houk and co-workers. Crago et al., 1976 observed that the stretch reflex was only apparent when subjects were asked to resist actively a perturbation. No response was observed when they did not oppose limb displacement. This led to the idea that the stretch was not required for involuntary maintenance of optimum muscle length, but rather involved in the maintenance of muscle stiffness. The servo-modulation theory was further expanded upon in later equilibrium control theories where it was argued that the brain did not need



to represent all the minute steps that are expressed in moving a limb from point A to B. Rather only the final end point B needed to be transferred from cortex to periphery and the intrinsic properties of the muscles stiffness maintained by the stretch reflex would take the limb from point A (Bizzi et. al., 1982). The advantage of this is again one of dimensionality reduction. Rather than the cortex needing to compute each millisecond of the movement through some complex neural code, the spinal apparatus could, through its intrinsic properties, execute the steps in between the start and the end of the movement. A further property of the stretch reflex apparatus, that of  $\alpha$ -  $\gamma$  co-activation would “smooth out” the movements profile since this makes the spindles highly sensitive to small perturbations. In theory therefore, a very crude motor program could be produced cortically which would be refined by the spinal reflex machinery.

*Evidence for a transcortical origin to the long-latency stretch reflex.*

The cortical origin of the long latency stretch reflex was the battleground for a series of physiological debates between Marsden and Matthews. Marsden et. al (1977a, 1977b) demonstrated that the long latency reflex was abolished by lesions of the dorsal columns or by focal lesions affecting the sensorimotor cortex. Furthermore, transcranial stimulation facilitated the response when this was applied at a latency expected to coincide with the stretch response arriving at the cortex (Day et. al 1991). Matthews, in contrast, argued that the longer latency was a function of involvement by slower conducting group II afferents. To prove this he set out to cool the arm and demonstrate that the increase in conduction time was consistent with a delay in group II conduction. In

fact, the results of his study were the reverse – the conduction delay was consistent with Ia afferent involvement and he conceded that the transcortical route was the most likely source for the late onset of the M2 response.

Further evidence also came from studies in patients with Klippel – Feil syndrome and studies in the non –human primate. In the Klippel – Feil patients, stretch of a muscle on one hand evoked long-latency responses in both sides, and a short latency response only in the stretched muscle (Matthews et. al., 1990). Cheney and Fetz (1984) examined CM cells in the primate motor cortex during a perturbations opposed on active wrist movements. These authors observed responses to the perturbation in single neurons that were consistent with the latency onset of the M2 response. This result suggested a direct involvement of CM cells in the M2 reflex.

*What is the function of the long –latency stretch reflex?*

One idea suggested by Philips (1969) was that the long latency reflex was generated in response to a mismatch between the expected and the actual stretch produced during a movement. For example, you go to pick up an object, which, on initial impressions appears heavy, but it is in fact much lighter than you anticipated. In response to this mismatch the muscle spindles respond to the increased stretch imposed upon them by the unexpectedly small load. In order to compensate and to prevent the object from slipping, the reflex recruits more cortical pyramidal neurons to drive the lower motoneuron pool. Marsden et al. (1972, 1975) and Day and Marsden (1982) examined linear movements produced by flexing the distal phalanx of the thumb against a constant force. When the

force was suddenly terminated an EMG burst consistent with a long latency reflex was elicited. These results were supportive of the hypothesis made by Philips that underestimation of the degree of stretch was driving the long latency response. One further assumption of Philips's hypothesis, that the gain of the long-latency reflex should be dependant upon the motor set, has also been demonstrated. Bonnet and Requin (1981) used a pre-cued reaction time task in which a single perturbation was delivered to the wrist at a random time between the warning and the go cue. These investigators described a progressive increase in the size of the transcortical reflex after the warning cue, which was maximal immediately prior to the cue to move. One major problem in the interpretation of the experiment by Bonnet and Requin is that the increase in transcortical reflex prior to the go cue may not have been a preparatory response to move, but rather a response to resist the perturbation. Since the probability of the perturbation was equal throughout the preparation period, as time elapsed, the subject would have been progressively more and more likely to expect a perturbation. It may therefore be the expectation of movement perturbation that up regulated the long latency reflex in these experiments.

Allowing for this re-interpretation of Bonnet and Requin's experiment, then the majority of experimental evidence suggests that the long-latency reflex may be developed for the online correction of movement or posture when the external environment exerts increased stretch upon the muscle. A final problem with this interpretation is whether the size and latency of the reflex are large and quick enough to be of any behavioural relevance. Since the reflex contribution to correction of perturbation is only applicable to small

disturbances (Marsden, Rothwell and Day, 1983); whether the transcortical reflex provides any greater benefit over and above the correction produced voluntarily is unknown. The exact relevance therefore of this reflex in motor control is unclear.

#### **1.4 Neural basis of the spontaneous electroencephalogram**

The EEG recorded from the scalp (or intracortically) displays rhythmic oscillatory activity that has been classically subdivided into frequency bands according to their dominant frequency components: delta (1-4 Hz), theta (4-6 Hz), alpha (8-12), beta (13-30) and gamma (40-60 Hz).

This introductory sub-chapter will introduce the concepts of how the electrical field potential is generated at the cellular level and how it is represented at the cortical surface. Three basic mechanisms will be presented as the basis for oscillatory activity in the EEG; intrinsic cell characteristics; intracortical connectivity, and thalamocortical resonance. Although these will be presented as separate mechanisms, it seems most likely that all three contribute in some way or another to the rhythmic characteristics of the EEG. Where relevant I will make specific emphasis with regards to beta oscillatory activity.

##### *Origin of extracellular field potential*

Despite the large amplitude of action potentials these are not thought to contribute to the extracellular field potential. Li and Jasper (1953), and also Li et. al., (1952) demonstrated

that the EEG could still be recorded during deep anaesthesia when no action potentials were generated. Theories of the basis of extracellular field potential have therefore argued that the slower rise time of post-synaptic potentials suggest that these are more likely to make a significant contribution. Despite the reliance upon synchronised neuronal firing for macroscopic field potential generation, action potentials would have to synchronise with 1ms precision to make a meaningful contribution. From a computational point of view this is a simple but important distinction. The field potential reflects the input to a cell population rather than its output.

Pyramidal neurons are thought to be the most important cellular contributors to the neocortical field potential. The reasons for this are that these cells are organised in a highly regular columnar manner, thought more likely to produce macroscopic field potential than the irregularly organised interneuronal population. Furthermore, pyramidal neurons receive divergent thalamocortical input required to synchronise multiple neurons for macroscopic field potential generation (Gloor, 1985).

An influential theory in the understanding of the cellular basis of the EEG has been in the conceptualisation that the pyramidal neuron can be viewed as a dipole. A dipole is formed when current flow causes two oppositely charged poles to form in distinct spatial regions. In the pyramidal neuron a dipole is typically formed between the basal dendrites and cell body and the apical dendrites. For example, when a series of synchronised EPSP's arrive at the apical dendrite depolarisation causes a net negative extracellular potential. This results in a flow of current within the extracellular space from the basal

towards the apical dendrites. If the extracellular potential were viewed from the pial surface, a field of negative charge would be observable (a current sink), whereas from the deeper cortical layers a field of positive charge would be seen (a current source). The voltage fluctuations recorded at the surface of the brain can be viewed in terms of the summed macroscopic sinks and sources formed by the pyramidal neurons in response to the balance of their inhibitory and excitatory input.

#### *How is the EEG represented at the surface of the scalp?*

In simple terms, the negative deflection of the extracellular potential could be viewed as an increase in neuronal excitability, whereas the positive reflect decreases (Speckmann and Elger, 2005). This becomes an oversimplification when recording from the surface of the brain, since the pyramidal neuronal dipoles do not generate one uniform dipole distributed equally across the neocortical surface. Instead dipoles may be formed in spatially discrete regions distributed *across* the scalp. This gives rise to the impression of discrete field potential generators. Furthermore, when recording within the brain ie. intracranially, the additional spatial resolution may result in the formation of dipoles across very small regions of the cortex caused by the convolved nature of the brains surface. Polarity reversal of the field potential may occur when potential is compared between a sulcus and a gyrus.

In all, the EEG recorded from the surface of the brain or scalp can be viewed in terms of changes in the synchronised pre-synaptic input to spatially discrete populations of

pyramidal neurons. However, because of the spatial organisation of cortical dipoles the relationship of the potential fluctuations to the precise nature of the neuronal input cannot be predicated with any accuracy.

### *Why does the field potential oscillate? – intrinsic properties of neurons*

One explanation for the oscillatory activity in the EEG is that neurons prefer to fire or prefer to receive input at specific frequencies. I will describe these types of neurons in terms of pacemakers or resonators respectively. The difference between a pacemaker and a resonating neuron is that the former can fire at its preferential frequency in the absence of input. In contrast, resonant neurons only display their frequency preferences when driven by sensory input (Hutcheon and Yarom, 2000).

The existence of pacemaker neurons in the CNS has been recognised for many years (for example the central pattern generators that drive locomotion). However, only recently has evidence derived from single neuron recordings suggested that pacemaker properties exist in neocortical neurons. Llinas (1991) recorded frontal neocortical neurons *in vitro* and described two sets of neurons in layer IV with intrinsic firing properties on depolarisation. In the first type, action potentials fired at a narrow frequency band of between 35 and 50 Hz. These were demonstrated to be inhibitory interneurons. In contrast, the second type which fired at a broad-band 10-50 Hz were morphologically unidentified. In both types subthreshold oscillations occurred at resting membrane potentials and were shown to be Na<sup>+</sup> dependant. *In vivo* intracellular recordings from cat visual cortex also argued for the existence of pacemaker activity. The “chattering cells”

recorded by Gray and McCormick (1993) fired 20 to 80 Hz bursts in response to visual stimuli and suprathreshold current injection. These were thought to be layer II/III pyramidal cells with diffuse connections projecting to layers I, II, III and V, indicative of a wide potential sphere of action within the cortical column. An interesting common feature of these two studies was the interaction of membrane potential with the bursting frequency. As the membrane became progressively more depolarised the frequency of the oscillations increased. These studies may suggest that the firing frequency of pacemaker cells is dependant upon their excitability level.

Of specific relevance to this thesis are the findings of Chen and Fetz (2005) who recorded intracellular activity from awake primates in M1. These authors described a subset of neurons with an intrinsic burst firing preference around 20Hz. Although morphological characterisation was not possible these cells fired with an after-hyperpolarisation of 30 ms similar to those recorded by Llinas. This after-hyperpolarisation property of a subset of M1 neurons has also been observed using indirect estimates from extracellular recordings (Wetmore and Baker, 2003).

The resonance properties of single neurons can be characterised by recording their firing responses to different inputs containing different predominant frequency components. The resonance of a neuron is therefore an index of how frequency selective a neuron is (Hutcheon and Yarom, 2000). Pyramidal neurons in the guinea pig display two frequency preferences. At resting membrane potential a 1- 2 Hz resonance is observed (Hutcheon et.al 1996). When depolarised the neurons respond best to inputs between 5 and 20Hz



(Gutfreund et al, 1995). The frequency of the oscillation generated by these inputs is dependant upon  $K^+$  conductance whereas the amplitude is  $Na^+$  dependant, suggesting two independent mechanisms. The frequency selectivity of specific cell types has been directly tested *in vitro* by Pike et. al (2003). These authors recorded from identified pyramidal and fast spiking interneurons in the hippocampus. Pyramidal neurons responded best to input at theta frequencies (4-8Hz) while fast spiking interneurons showed frequency selectivity at 25Hz.

In all, the evidence from both *in vivo* and *in vivo* experiments suggests that intrinsic properties of neurons may be in part responsible for the field potential fluctuations witnessed in recordings of the EEG. It seems likely that if neurons have frequency specific input preferences then there must be some set of neurons that generate the frequency of preference (ie. pacemakers) for them to respond to. The existence of both pacemaker neurons and resonant neurons in the thalamus may argue for some sort of cortico-thalamo-cortical loop (Puil, et. al , 1994; Ribary et. al., 1991). The empirical evidence for this will be presented below.

#### *Why does the field potential oscillate? – intra-cortical networks.*

Neural oscillations can be synchronised with almost zero phase lag over considerable neural distances (Roelfselma et. al., 1997; Ribary et. al., 1991). Experimental evidence from *in vitro* hippocampal preparations and computer modelling have suggested that cooperativity between neuronal networks may be able to explain these features of the EEG.

The most simple model applied in the consideration of network oscillations is one of recurrent inhibition. In his olfactory bulb model Freeman described the alternation in pyramidal and inhibitory neuron firing with a delay of half the period of the network oscillation (Eeckman and Freeman, 1990). In contrast, during hippocampal gamma oscillations, no phase delay exists between the firing times of these two types of neuron (Bragin et. al, 1995). The mechanisms behind this zero phase locking are thought to be the consequence of specific synaptic and electrical (gap junction) relationships between large inhibitory and excitatory networks (Jefferys et. al., 1996).

Whittington et al., (1995) first described the ability of inhibitory (GABAergic) interneurons to generate gamma (40Hz) oscillations in the absence of metabotropic glutamate neurotransmission. Furthermore, the frequency of the gamma oscillation was dependant upon the excitatory drive to the interneuron and the resulting length of the IPSP. In the models provided by these authors, it is the intrinsic properties of the interneurons that entrain the pyramidal neurons to their resonant frequency in response to afferent input (Jeffereys et. al., 1996; Whittington and Traub, 2003). Two key issues seem to arise in these models. Firstly for the entrainment of pyramidal neurons to high frequency oscillations peri-somatic inhibition is essential. In contrast, lower frequencies can be driven by input into more distal dendrites (Whittington and Traub, 2003). A second key factor in the stability of the oscillation is the homogeneity of both the excitatory input to the inhibitory interneurons and the inhibitory drive to the pyramidal neurons. When simulations of excitatory or inhibitory activity are allowed to become

more heterogeneous the oscillation breaks down (Traub, 1996; White et. al. 1998). One possible mechanism to produce coherent input to the network may be the pacemaker neurons described above (Whittington and Traub, 2003). However, the sensitivity of these oscillations to gap junction inhibitors suggests that electrical rather than chemical transmission may be key to the stability of network oscillations (Hormuzdi et. al., 2001; Traub et. al., 2001; Draguhn et. al., 1998). Gap junctions are located on pyramidal cell axonal collaterals (Traub et. al., 2001) and form connections with the dendrites of GABAergic inhibitory neurons (Tamas, 2000). It seems therefore, that the properties of electrical conduction between neurons may provide these networks with the ultra-fast and spatially distributed conduction properties required to explain zero phase lag over large (several mm) intra-cortical distances (Schmitz, et. al., 2001).

To what extent can these models of hippocampal gamma oscillations be extended to beta oscillations in the motor cortex? Considering the differences seen between Freeman's model in the olfactory bulb and the mechanisms of hippocampal oscillatory generation, caution may be required before assuming that the mechanisms are generic across different brain regions. Nevertheless, some interesting differences have emerged from *in vitro* work suggesting that distinct mechanisms may be at work in the emergence of these different activities. Traub et. al. (1999) delivered tetanic stimuli to hippocampal slices; with increasing stimulus intensity the initial evoked gamma activity made a transition to beta activity. This transition was associated with the emergence of EPSP's between pairs of non-monosynaptically coupled pyramidal neurons. Interestingly, the inhibitory neurons

recorded remained firing at gamma frequency with the pyramidal neuron pairs firing on every second cycle of the interneuron gamma.

More recently, *in vitro* recording from rat parietal cortex slices has identified intrinsically bursting pyramidal neurons which fire at 20 –25 Hz. This field potential was generated in deep layers since the oscillation persisted after cutting through layer IV and was shown to be specifically dependant upon gap junctions between these neurons. Although GABA agonists enhanced the amplitude of the oscillation, they persisted after both GABA<sub>A</sub>, GABA<sub>B</sub> and AMPA blockade (Roopun et. al., 2005). Intracellular recordings from these neurons revealed a characteristically large depolarising after potential; note that the neurons recorded by Chen and Fetz (2005) had pronounced *hyperpolarizing* after-potentials. Many different features of the experimental preparations used in the two studies could account for this difference.

In summary, the data from *in vitro* studies have provided some important conceptual advances in our understanding of intra-cortical network processes in oscillatory generation. The difficulty with recording from neocortical slices has meant that there is currently little precise knowledge of beta oscillatory generation in the motor cortex specifically. Differences between brain regions and potentially between neocortical regions may exist in terms of the mechanisms of intra-cortical network oscillations. It seems likely though that some of the most fundamental mechanisms such as electrical transmission are generically used across different brain structures.

*Why does the field potential oscillate? – subcortical-cortical networks.*

A very dramatic change in the EEG occurs between sleep and wakefulness. During non-REM stages of sleep the EEG is characterised by large amplitude slow wave oscillations around delta frequencies while during states of arousal fast oscillations are observed (Steriade, 2005). This global transition in the brain state is thought to be mediated by changes in the properties of thalamocortical projection neurons.

Although initial investigations dismissed the thalamus as an important contributor to cortical rhythm generation (Gray et. al, 1989 and Singer and Gray, 1995), Steriade was the first to describe the existence of 40 Hz bursting thalamocortical neurons in the centrolateral nucleus of the thalamus (Steriade et. al., 1993) and in layer VI corticothalamic neurons (Steriade, 1997; Steriade et.al, 1998). Further work by this group demonstrated that the cortical fast oscillations were phase locked to thalamocortical bursting, reinforcing the concept of a loop phenomenon. Frequency specific potentiation of the corticothalamic EPSP's occur (Lindstrom and Wrobel, 1990), suggesting that amplification within a cortico-thalamo-cortical loop by 30-50 Hz oscillations may be important in distant synchronisation of cortical areas (Llinas and Ribary, 1993).

### **1.5 Origins of Cortical Evoked potentials**

In the previous sub-chapter I have introduced the concept of spontaneous neural potential fluctuations (which are oscillatory in nature) and presented some of the reasons for their

emergence. Neural field potential can also be described as “evoked”. This is a misleading term since clearly all spontaneous neural activity seen *in vivo* is evoked by some sort of stimulus, however in the case of evoked potentials the properties, and importantly the timing of the stimuli are known. Thanks to the temporal fidelity and reproducibility of neuronal responses, the response to a stimulus can be observed in a single trial or after averaging to the stimulus onset (depending upon the signal to noise ratio of the EEG). The following discussion will focus mainly upon the origins of somatosensory evoked potentials (SEP) evoked by stimulation of the median nerve.

*Cortical regions involved in the early SEP components.*

If the responses to median nerve stimuli are recorded from the scalp or intracortical electrodes arranged tangentially to the central sulcus, voltage deflections are observed at a latency of between 20 and 40 ms after the stimulus onset. The polarity of these responses reverses at the central sulcus. In the precentral or frontal electrodes the initial response is a positive deflection at a latency of 20-22 ms, known as the P20. A similar method of nomenclature is applied to the other components. Therefore the post-central component is known as the N20, and the subsequent negative and positive deflections at 30ms are the N30 and P30 observed over the pre and post central gyri (or frontal and parietal scalp positions) respectively (Allison et. al., 1991; Mauguiere, 2005). An intermediate latency complex is also recorded directly over the central sulcus at 25 and 35 ms with positive (P25) and negative (N35) polarities (Allison et. al., 1991; Mauguiere, 2005).

Although consensus has mostly been reached as to the cortical (rather than subcortical) origin of these responses (thalamic lesions abolish the 20 ms responses and those after [ Kimura and Yamada, 1982; Mauguiere et. al., 1983; Allison et. al., 1991 ] ), the exact region of the cortex involved has been, and remains a source of controversy (Allison et.al., 1991). The main point in question has been whether the different polarities of the responses seen pre- and post centrally can be explained by two separate generators or one. Of the two theories proposed, the single generator theory has emerged as the most prominent. I will summarise the basis of these two different arguments and the evidence for and against them below.

As highlighted above, neuronal field potentials are generated by current sources and sinks formed between the apical and basal dendrites of pyramidal neurons. In the two source model one separate current sink and a separate current source are generated in the pre-and post central gyri in parallel to (radial) the scalp / cortical surface (Desmedt and Cheron, 1980). In contrast, the single generator model argues that the polarity difference results from a single generator within the posterior bank of the central sulcus (area 3a), (Allison et. al., 1982). The rationale of these investigators was that by residing within the central sulcus, tangentially oriented to the brain surface, the difference in polarity arose from the electrodes “viewing” the same dipole formed by the pyramidal neuron layer from a tangential orientation. In other words, when the pyramidal neuron dipole was viewed from the post central sulcus it would always be opposite in polarity from the pre central because it’s view was biased by the apical dendrites. In contrast, the post central electrodes were viewing a basal dendrite biased field potential.

One prediction that could be made from the two source model was that if the generator is arranged radially then polarity reversal should occur below the cortical layer generating the evoked field. This was shown not be to the case by Allison et. al., (1989). Strong evidence for a single generator of the 20 and 30 ms potentials has come from lesion studies in humans and primates. Following excision of the motor cortex in a patient with epilepsy the P20-N30 complex was unaffected (Allison et. al 1991). This result was reconfirmed in primates and extended by demonstrating that both pre and post central complexes were abolished on removal of area 3a (Allison et. al., 1991). Finally the later P25-N35 complex (or at least its monkey analogue) was shown to be abolished by removal of the crown of the central sulcus (areas 1 and 2) suggesting that these responses were being generated by a separate dipole to the 20-30ms complex (Allison et. al., 1991).

In summary, current opinion argues for a single tangentially orientated dipole located in area 3a as the source of the 20 and 30 ms responses; with a second, radially orientated dipole in areas 1 and 2 being principally responsible for the 25 and 35 ms complexes.

#### *Peripheral receptors responsible for the SEP*

Due to its inaccessibility, the contribution towards the SEP made by area 3a (and by inference muscle spindle input) has not been tested with the definitive lesion studies noted above. It is unsurprising therefore that there is some uncertainty as to the relative proportions that muscle spindles versus cutaneous receptors make to the SEP. Indirect assessments have been made using peripheral nerve microstimulation. Halonen et. al.,



(1988) recorded scalp SEPs in response to stimulation of the superficial (cutaneous) and deep (muscle spindle) radial nerves. Cortical responses were better defined when the cutaneous branch was stimulated. In afferents of the median nerve studied by Gandevia and Burke (1990), a similar disparity was observed; the N20 –P25 amplitude was 7 times smaller when the thenar muscle afferents were stimulated compared to the cutaneous afferents. Although earlier studies suggested a central role of area 3a in the generation of the SEP (Gandevia et. al., 1984) the weight of evidence from microstimulation studies would argue for a minority role for muscle spindle afferents. Nevertheless, some caution is required before eliminating spindles as a meaningful source of input. Considering the amplitude dependence of the N20-P30 complex upon the morphology of the post-central sulcus (Wood et. al., 1988); it would not seem implausible that the deep location of area 3a reduces its volume-conducted contribution to the surface recorded SEP.

### **1.7 Oscillations in the motor system.**

Jasper and Penfield wrote in 1949 that the characteristic feature of the pre and post central gyrus was a rhythmic potential occurring at 20 times per second (Penfield and Jasper, 1949). This typically reduced in amplitude during and prior to voluntary movement but was maintained during postures such as clenching of the fist and at rest. Their descriptions of the peri-rolandic beta rhythm summarise the most salient features of what is recognised about this activity today, despite the passage of over fifty years. In the next section I will describe more recent work which has attempted to understand the function of these oscillations in motor control.

### *Oscillatory activity in M1 in relation to movement in the primate*

The interest in oscillatory activity that emerged from ideas of sensory binding in the early and mid 90's inspired work on a "motor binding" correlate. The initial proposition that oscillations might "bind" the disparate components of the motor cortex during a movement into a functional whole was confounded by the lack of oscillatory activity during movement *per se*.

Murphy and Fetz (1992, and, 1996) recorded from M1 and S1 while monkeys made freely moving "exploratory" movements and trained flexion-extension movements. Beta oscillations were observed in both M1 and S1 LFPs and were shown to be phase locked over large cortical distances (18mm within the precentral, 20mm across the central sulcus [estimated for cortical unfolding]) and to the firing of MUAPs. Back averaging the EMG to the peaks of the oscillations revealed some causal relationship suggesting that the oscillations could entrain the cortical output neurons. This was of some interest since oscillation polarity reversal occurred at 800µm, leading these investigators to conclude that the superficial layers, and the associated cortico-cortical fibres in these layers, may be generating the oscillation. The incidence of oscillatory activity was greatest when the monkeys were making exploratory movements for an object located outside of their visual field, suggesting that the oscillation was involved with sensorimotor integration.

Sanes and Donoghue (1993) and Donoghue et. al (1998) concentrated their efforts on recording precentral neurons and LFP during a precued finger force task. This task

provided a more specific test of the contribution oscillations made towards preparing, initiating, or executing movements. The general theme from these experiments was that there was little explicit association between the execution of movement and oscillatory activity. This was because, “the suppression of oscillations at the onset of movement was ubiquitous”. Several interesting points came from these recordings nonetheless. Firstly suppression of oscillatory activity was variable, particularly prior to fine finger movements. Beta oscillations often continued into the initial phase of the task before being suppressed, suggesting that these may have been generated by “set” cells; with discharge patterns related to movement preparation. Indeed, oscillations in these experiments often became prominent in the preparation period prior to movement onset (Note that this has also been observed of beta oscillations in the cerebellum [Courtemanche et. al., 2003]).

### *Cortical drives to muscle*

Indirect evidence from paired motor unit recordings suggested that there was a central drive to muscle at the same frequency of the oscillations recorded in the primate studies described above (Datta et. al, 1991; Farmer et. al, 1993a, 1993b). The evidence for direct cortical drive to muscle in the beta range was first demonstrated by Conway et. al (1995) and later by Salenius et. al. (1997) and Baker et al., (1997) in the monkey. These first studies made a simple association between the level of contraction and the dominant cortical drive. Moderate contractions were associated with beta coherence, whereas strong contractions were associated with drive to muscle at around 40Hz (Brown et. al.,

2001). A final 10Hz activity, observed during slow finger movements (Vallbo and Wassberg, 1993), was thought to arise from a loop involving the cerebellum and motor cortex (Gross et. al., 2002). The central origin of this component is confounded by the fact that physiological tremor at 10Hz is thought to arise from the intrinsic properties of lower motoneurons (Lippold, 1970, Matthews, 1997). It should be noted however, that recent experimental and modelling evidence suggests that beta oscillations, in muscle, may also be accounted for, in part, by similar peripheral mechanisms (Moritz et. al., 2005).

One possibility is that the oscillations observed in muscle, coherent with the motor cortex, are simply an epiphenomena of cortical discharge. In other words, the muscle is a passive recipient of the cortical discharge at 20Hz. The experiments of Kilner et.al, (2000) would argue to the contrary. These authors extended previous observations, that during a precision grip task, the coherence was highest during the hold phase and was abolished during the ramp (Kilner et. al., 1999; Baker et. al. 1997). Although these results could be explained through task dependant changes in power, the extent of the coherence was shown to be dependant upon the compliance of the levers being manipulated (Kilner et. al., 2000). This increase in coherence seen when highly compliant levers were manipulated was, critically, independent of any change in power in either the MEG or EMG. Therefore, the degree of phase locking between the lower and upper motoneurons in the beta range was dynamically modulated according to the properties of the object being manipulated.

### *Afferent mechanisms involved in cortico-muscular coherence*

By inference, the previous section would suggest that the phase relationship between the muscle and the cortical oscillations is not a constant variable determined by the conduction time of the corticospinal tract. The idea that the coherence may be a function of afferent feedback emerged from studies where beta coherence was reduced between muscles by local anaesthesia (Fisher, et. al., 2001), and was absent in a patient with peripheral neuropathy (Kilner et. al., 2003). Riddle and Baker (2005) have recently explored the affects of cooling the arm upon cortico-muscular coherence. The changes in phase delays estimated from the coherence analysis could not be accounted for solely from changes in the efferent conduction time. These authors concluded a mixture of efferent and afferent processes might be critical for determining the phase relationship (and coherence) between cortex and muscle discharge. The eventual extent of cortico-muscular coherence being dependant upon the interaction of the descending volleys with the intrinsic resonance of the monosynaptic pathways; one cancelling the other out and vice versa or phase locking depending upon the afferent input.

Evidence to suggest that afferents also represent beta oscillations in their firing activity also comes from a recent study by Baker et. al., (2006). Recordings from the dorsal root ganglia in the monkey revealed a peak in the power spectrum at around 20Hz which showed bi-directional coherence between the unit and muscle EMG (ie. the unit was both detecting and driving, presumably through monosynaptic pathways). Interestingly, the

coherence was specific to group of Ia afferents; no coherence was observed between cutaneous afferents and the muscle.

The following excerpt from Adrian (1941, [page 173]) is historically interesting in this context:-

*“In light anaesthesia in addition to rapidly oscillating discharges there is often continued noise of impulses in the whole of the somatic receiving area [S1]. The noise is not as loud as that due to a tactile volley, but it seems to be caused by a persistent discharge from the thalamus, for a wire electrode in the white matter will pick up continued trains of impulses at 10 – 25 a second. It is uncertain whether they correspond to particular afferent signals from the periphery... They may represent a generalised excitation from the proprioceptors...”*

#### *Evidence for pyramidal neuron involvement in beta oscillations*

Corticomuscular coherence must, by definition, involve the pyramidal output neurons. Studies in primates have demonstrated weak coherence between single pyramidal neurons and the cortical field potential. Once the non-linearity of neuronal spiking was taken into account, models of multiple weakly coherent pyramidal neurons could account for much of the beta field potential (Baker et. al., 2003). To establish whether the pyramidal neuron was an intrinsic component of the rhythm generating machinery, Jackson et. al., (2002) delivered stimuli to the medullary pyramids in awake monkeys.

The cortical beta LFP was reset by stimulation and these authors concluded that the resetting was induced by antidromic depolarisation, which could only reflect the incorporation of the pyramidal neuron into the circuit involved in beta oscillation generation. A human correlate to this result has also been observed by Paus et.al. (2001). Delivering TMS at intensities lower than motor threshold, resetting of the beta activity could be seen after the stimulus, lasting in some trials for several cycles.

### *Tremor*

Two frequency components characterise the physiological tremor spectra: one at 8-12Hz and another at 13-35 Hz. Original studies on the origins of these activities suggested that the 13-35Hz was a resonance phenomenon of the mechanics of the limb, since, on loading the frequency decreased, whereas, the 8-12Hz did not modulate its frequency on loading and was deemed of central origin (Stiles and Randall, 1967). Spinal resonance at 10Hz was suggested by Lippold (1970) to contribute to the 10 Hz peak since prodding the outstretched finger caused cyclic oscillations in the finger at the same frequency as that of the subject's physiological tremor. This was refuted by others since the frequency of the oscillation is independent of the length of the reflex loop (Halliday and Redfearn, 1956; Elble and Randall, 1976; Fox and Randall, 1970).

It is now recognized that the tremor peaks both at 10 and 20 Hz can be attributable to motor unit synchronisation (MacAuley et. al. 1997; Halliday et. al. 1999; Datta et. al, 1991; Farmer et. al, 1993). Halliday et. al, (1999) have estimated that between 20 and

70% of the tremor can be causally related to motor unit synchronisation. Since synchronisation can be in turn be related to common motoneuronal innervation by a descending cortico-spinal neuron (Kirkwood and Sears, 1978), the evidence presented above for cortical drives to muscle must argue for a meaningful contribution from a common cortical drive to the physiological tremor peaks. Moritz et. al., (2005) have provided evidence to suggest that synchrony between motor unit firing times can contribute to the 20Hz peak seen in the tremor, independently of a central drive. Indeed, the intrinsic firing properties of motoneurons were also thought to contribute to the 10 Hz peak (Matthews, 1997). Physiological tremors must be viewed therefore in terms of the complex superimposition of *both* peripheral and central resonance phenomena on the motoneuron firing pattern.

#### *Can the spinal cord generate beta oscillations?*

Much of the previous discussion has concentrated on the evidence pertaining to the cortical contributions to ~20Hz oscillations seen in muscle. A critical point to make here is that oscillations in muscle may arise in muscle at beta frequencies *without* a common cortical drive. This is exemplified by the case report of Norton et. al. (2004) who observed coherence between pairs of leg muscles at 16Hz in a patient with orthostatic tremor secondary to spinal cord transection. Therefore, it is important to bear in mind that the peripheral oscillatory activity studied in the experimental sections of this thesis, may arise independently of the cortex, albeit through mechanisms that are poorly understood.



### *Oscillations in subcortical brain regions*

Beta oscillations have also be observed in LFP recordings from the basal ganglia, cerebellum and thalamus in humans after undergoing functional neurosurgery (Brown et. al, 2001; .Marsden et. al, 2001; Levy et. al., 2002; Cassidy et. al., 2002; Williams et. al. 2002, Dostrovsky and Bergman., 2004) including the subthalamic nucleus and globus pallidus in humans; and from the striatum and cerebellum in monkeys (Courtemanche et. al., 2003a; Courtmanche et. al, 2003b; Soteropoulos and Baker , 2006) . The overall consensus from these recordings is that the oscillations are coherent with the cortex and show the characteristic desynchronisation around movement. A distributed system of oscillators within the motor system, with the beta oscillation as its signature, may argue for a generic role in effective communication between distributed regions including the corticospinal system.

### **1.8 Physiological functions of oscillatory activity in the brain.**

The only explicit empirical demonstration that oscillations are essential for effective brain function has come from experiments in the olfactory bulb of the locust. In this preparation MacLeold et.al, (1996) demonstrated that blocking GABA receptors could reduce oscillatory activity without affecting the rate coding functions of the neurons recorded. The effect of losing oscillatory activity was a reduction in the sensitivity of neuronal response to presentation of different odours. This was strong evidence to suggest that oscillations were essential to the effective function of this group of neurons.

In higher organisms, the complexity of the neuronal systems involved makes the ability to pharmacologically dissociate oscillatory activity from normal neuronal function far harder. Thus, the ultimate experiment of demonstrating that higher brain function is impossible without oscillatory activity has not yet been attempted. The development of mice with gene knockouts for proteins involved in oscillatory generation is therefore keenly awaited (Sejnowski et. al., 2006). Most of the data, which has inspired theories as to the function of oscillations in the brain, is consequently correlative in nature. In the next section I will described some general theories of oscillatory function in the brain and then some more specific theories with regards to oscillatory function in the corticospinal tract.

*Some general theories of oscillatory function in the brain.*

The binding problem, i.e., how can sensory features represented by several neurons be integrated into a single percept, was argued by Gray and Singer to be solved in part by oscillating the neurons in one coherent cell assembly. Experiments performed in cats, recording in visual cortex, demonstrated that pairs of neurons with common response properties to a visual stimulus were more likely to fire phase locked to the gamma oscillation in the LFP than pairs that did share a common response to a visual stimulus (Singer and Gray, 1995). The inference of these experiments was that the neurons were bound together by a common LFP oscillation. Indeed, this binding through oscillations has been postulated to be a critical procedure in the emergence of conscious experience (Gray and Singer, 1989; Singer, 1999).

A further way in which oscillations could aid in the representation of sensory input is through improving the reliability of neuronal spiking. An emerging consensus suggests that neurons may represent input by precise spike timing (Hopfield, 1995; Mainen and Sejnowski, 1995). The accuracy of neuronal spiking is now known to be dependant upon the intrinsic frequency preferences of the neuron; input driven into a neuron at its preferred frequency is more accurately represented in its output (Hunter, et. al., 1998; Fellous et. al., 2001; Schaefer et. al., 2006). This enhancement of the representation of temporal information may also be critical for associative “hebbian” reinforcement of synapses, since the precise relationship between correlated pre and post-synaptic firing is thought to determine the degree of synaptic reinforcement (spike timing dependant plasticity [Froemke and Dan, 2002]).

Correlated neuronal firing has been recognised as a basis for improving the probability of synaptic transmission to down stream neurons (Abeles, 1991; Salinas and Sejnowski, 2001). Neural oscillations, which reflect correlated post synaptic potentials (see section 1.4), may therefore, provide a basis for promoting the flow of information within or between brain regions (Salinas and Sejnowski, 2001). This idea has led some investigators to suggest that oscillations may represent the neural correlate of attention (Fries et.al., 2001a). Recordings from monkey visual cortex during a selective visual attention task have provided some good evidence for this hypothesis. When a monkey attends to different parts of a fixed visual stimulus the spike – LFP synchrony is low; when the monkey attends to the stimulus within the receptive field of the neurons recorded the spike – LFP synchronization increases (Fries et. al., 2001b).

### *Some theories on the role of oscillations in motor control*

Baker et. al., (1999) provided empirical and theoretical evidence to argue that corticospinal beta oscillations may be an optimal mechanism for corticospinal interaction during postural contractions. These investigators argued that a lower mean firing rate could be used to drive the lower motoneuron pool if the neurons were synchronised by a descending oscillatory drive. This has been further extended by Shoffelen et. al (2005) who described the emergence of corticospinal gamma oscillations with the increasing expectancy to move. The use of oscillations as a means to promote information flow through correlated discharge has been the most profitable model so far. The idea that this might represent some form of motor attention has also been suggested since corticomuscular beta coherence is dependant upon attention and the precision required for the task (Kristeva Friege et. al., 2001). In contrast, although non- oscillatory , stochastic synchrony has been shown to “bind” muscle fields (Jackson et.al, 2003), no obvious organisation of muscle at the cortical level has been demonstrated. Murthy and Fetz (1996), could not find any obvious relationship between the locking of neurons to the beta rhythm in M1 and their organisation of their output to muscle.

In summary, in contrast to the evidence for oscillations involved in sensory cortical function, a definitive role in motor control, certainly in terms of motor output, is yet to be established.

## **1.8 Pathological roles of oscillations in movement disorders.**

Movement disorders can be broadly considered in terms of two categories (although features of both category can co-exist): Hyperkinetic; where the diseased state is characterised by involuntary movements including tics, tremor, dyskinesia, chorea, jerky (myoclonic) or dystonic movements. Of the second category, the hypokinetic movement disorders, Parkinson's disease is by far the most important in terms of its prevalence. The biochemical causes of classical Parkinson's disease are well recognised, however, the pathophysiological chain of events that lead to the three cardinal features of this disease, namely; tremor, bradykinesia and rigidity, are poorly understood.

The resurgence of interest in neurosurgery for the control of symptoms in Parkinson's disease has led to some critical testing of the previous anatomical models (DeLong, 1990). Specifically, the idea that changes in the balance of inhibition and excitation between basal ganglia nuclei should alter the average firing rate has not been proven in electrophysiological recordings of the basal ganglia in patient recordings or in MPTP treated monkeys (Hutchison et.al, 1994; Wichmann et. al., 1994; Levy et. al., 2001). Instead of firing rate modulation on dopamine depletion, the most common feature reported in these recordings is a change in the pattern of neuronal firing. Neurons in the basal ganglia and cortex tend to burst at frequencies locked to the Parkinsonian tremor (Hutchison et. al., 1997, 1998; Levy et. al., 2000, 2002). This result is quite intuitive when applied to a symptom that is oscillatory by definition. However, in the so-called akinetic-rigid patients, exaggerated beta frequency oscillations are observed off dopamine

replacement therapy and are suppressed on drug administration (Brown et. al., 2001; Levy et. al., 2002). Beta oscillations have been argued by Brown (2001) to be a neurophysiological index of an anti-kinetic state. The following description will summarise the evidence for this theory.

#### *Beta oscillations as an anti-kinetic state*

As described above, the suppression of beta activity is an almost ubiquitous event prior to movement initiation in the motor cortex. This event related desynchronisation can also be extended to the basal ganglia subthalamic nucleus. In Parkinsonian patients the cortical (Wang et. al., 1999) and subcortical (Cassidy et. al., 2002) suppression of beta activity is impaired and is improved on L-DOPA administration (Doyle et. al., 2004). Furthermore, the average and single trial reaction time to movement is inversely correlated with time of beta activity suppression within the basal ganglia (Kuhn, et. al, 2004; Williams et. al., 2005). Brown et. al. (2004) have demonstrated that HFS of the subthalamic nucleus suppresses beta activity within the globus pallidus, implying that the mechanism of its effect may be in the suppression of the beta oscillatory activity and its associated antikinetic state.

Since beta oscillations are coherent with the cortex with phase delays consist with conduction from cortex to STN (Williams et. al., 2002), do cortical beta oscillations play a role in the expression of the disease symptoms? This hypothesis was tested by Silberstein et. al., (2005) who examined the degree of cortio-cortical coupling between

EEG electrodes and related this index to the clinical state and effects of HFS in these patients. The degree of cortico-cortical coupling was strongly related to the severity of the disease and was reduced both by HFS and dopaminergic drug administration.

These results and the results described above, may suggest that the over expression of cortico-basal ganglia resonance at beta frequencies, may produce a cortical state which is incompatible with effective movement parameterisation.

### **1.9 Principle aims of this thesis.**

The principle aims of this thesis are to further understand the physiological mechanisms that contribute to bradykinesia in Parkinson's disease. To understand further the causal relationships between oscillatory activity and parkinsonism a better knowledge of the properties of physiological oscillatory activity in the corticospinal tract is necessary. Through understanding the properties of beta activity associated with the healthy corticospinal tract, it may be possible to understand why beta activity is so strongly associated with bradykinesia in Parkinson's disease. Specifically the aims are threefold:

1. To demonstrate that physiological corticospinal beta oscillations in the non-Parkinsonian state are associated with the pathophysiological hallmarks of Parkinsonism: this would strengthen a causal relationship and weaken the argument for the oscillation as a tightly correlated epiphenomena.

2. To investigate the afferent (sensory) and efferent (motor) properties of this brain state in healthy humans.



## **Chapter 2: Experimental and Analytical Methods.**

The results presented in this thesis were derived from experiments made from healthy subjects or in the case of the electrocorticograms, from patients who had undergone functional neurosurgery for either chronic pain syndrome or Parkinson's disease.

In all experiments subjects gave their informed written consent and were studied according to local ethics committee guidelines.

### **2.1 Signal analysis**

Characterisation of the oscillatory signals was performed both off-line in the frequency and time domains using either Fourier or wavelet based methods in Matlab version 7.01 (Mathworks, Inc. USA).

#### **2.1.1 Fourier derived estimates of power and coherence**

The frequency content of continuous signals, (ie. those with a constant period such as radiowaves), can be described simply in terms of the signal's product with a sine and or cosine function with a specific frequency. If this Fourier transform is repeated using cosine and sine waves of different frequencies a frequency spectrum  $X(f)$  of signal  $x(n)$  is derived. Non-stationary, discrete signals such as those recorded in this thesis are typified by changes in frequency on a small time scale relative to the period of the oscillation (i.e. the frequency of the oscillation can change after only a few

cycles). The application of a continuous Fourier transform to such signals which modulate their period discretely in time produces erroneous estimates of the frequency content of the signal. The preferred method for analysing neuronal activity in the frequency domain therefore involves the use of so called discrete Fourier transforms (Halliday et. al., 1995) DFT;

$$X(f) = \sum_{t=1}^T x(t) e^{-2\pi i f t} dt, \quad (1)$$

where  $t$  is the sampling position within a discrete window of samples with length  $T$  and a sampling interval of  $dt$ . The DFT is also known as the exponential Fourier transform (Jordan and Smith, 2002), hence the term  $e$ . This term produces a waveform of frequency  $f$  which is multiplied with the signal  $x(n)$  to produce the complex spectral estimate  $X(f)$ . The term  $i = \sqrt{-1}$  endows this final property of  $X(f)$ , which will be important in the derivation of phase described below.

Using the DFT algorithm non-overlapping, discrete windows of spectral estimates of a signal can be made. The frequency resolution of  $X(f)$ ,  $R$ , is equal to the sampling rate  $fs$  divided by the number of samples in the DFT window of length  $T$  (ie.  $R = fs/T$ ). The maximal discernable frequency equal to  $fs$  divided by 2. Therefore the frequency resolution of the estimates can be improved by using larger values of  $T$  to estimate  $X(f)$ . However a compromise between the temporal and frequency resolution must be made since using large windows for high frequency resolution defeats the purpose of using a transform which can be defined discretely in time. In addition the length of  $T$  is typically

designed to match the quasi-stationarity of the EEG which is of an interval between 1 and 2 seconds. In this thesis values of  $T$  equal to  $2^9$  or  $2^{10}$  were used and are defined in the appropriate chapter. (Using values of  $T$  with  $2^y$  increases the computational efficiency of the DTF).

The power spectrum  $P_x(f)$  or autospectrum  $A_{xx}(f)$  provides an averaged estimate of the signal's "energy" at different frequencies after it has been divided up into windows of equal length and the DFT has been performed. These two indices are exactly the same, however, the autospectrum is traditionally used in further extrapolations for the estimation of coherence  $Coh_{xy}(f)$  since it is conceptually related to the cross spectrum  $C_{xy}(f)$ , therefore I will define them both for clarity;

$$P_x(f) = \frac{1}{N} \sum_{n=1}^N |X_n(f)|^2, \quad (2)$$

and

$$A_{xx}(f) = \frac{1}{N} \sum_{n=1}^N X_n(f) X_n^*(f), \quad (3)$$

where  $N$  is the total number of windows of ( $T$  length) and  $X_n(f)$  is the DFT estimate for window  $n$ . Finally  $*$  is the complex conjugate which effectively produces a positive, real value for  $A_{xx}(f)$ .

Coherence is an index used to establish the extent to which two signals are coupled (note that coherence can be established between more than two signals, but for simplicity here I will only describe the bivariate case). This is of considerable interest in neuroscience where two brain regions may contain neural activity with similar frequency spectra and the question of interest is whether these similarities are the consequence of two independent processes, or, the consequence of one process common to two brain regions. A simple analogy for the null hypothesis that there is no coherence between two signals would be two cortical regions with separate pacemaker activity (with the same frequency). Alternatively, two brain regions may be coherent because they are receiving common synaptic input from the same subcortical generator. The basic difference between these two examples is that although there may be common power between the two brain regions, because the generators are independent, the phase of the oscillatory signals will be independent and therefore random. In contrast, in the example where there is a common subcortical input to the two brain regions the phase of the oscillations produced by both regions should be related because they are being driven by the same input. It is this question of whether the phase of the signals is related or independent that coherence is an index of and whether there is co-modulation in the amplitude of the two signals. More specifically, coherence is the ratio of the phase locked power between two signals to the total amount of power that both signals possess between them.

Formally the coherence  $Coh_{xy}(f)$  at frequency  $f$  between signals  $x(n)$  and  $y(n)$  can be expressed as the ratio of the cross-spectrum squared  $(C_{xy}(f))^2$ , to the product of the two signals autospectra;

$$C_{xy}(f) = \frac{1}{N} \sum_{n=1}^N X_n(f) Y_n^*(f), \quad (4)$$

N is the number of DFT windows as before and the coherence is,

$$Coh_{xy}(f) = \frac{\left| \sum_{n=1}^N C_{xy}(f) \right|^2}{\sum_{n=1}^N A_{xx}(f) A_{yy}(f)} \quad (5)$$

By squaring the cross-spectrum and therefore balancing equation 5 the coherence value is bound between 0 and 1. Coherence values are considered significantly different from what would be expected of two independent signals at the 100% $\alpha$  significance level, when values are greater than  $1 - (\alpha)^{1/(N-1)}$ .

The argument of a complex number (complex argument), such as the cross-spectrum produces an angle which is formed by the real and imaginary parts of the number in polar coordinates. In the frequency domain the complex argument of the cross-spectrum is known as the phase spectrum,  $\phi_{xy}(f)$ ;

$$\phi_{xy}(f) = \tan^{-1} \frac{\sum \Im(C_{xy}(f))}{\sum_{n=1}^N \Re(C_{xy}(f))} \quad (6)$$

Where the  $\Re$  and  $\Im$  are short hand for real and imaginary numbers respectively. From the phase spectrum of two signals an estimate of the conduction delay can be estimated. The basis for this conduction delay estimate is that coherence will be present across several frequencies around a central peak. If a constant conduction delay is assumed then the phase across coherent frequencies should be greater for higher frequencies (since the delay represents a greater proportion of the oscillation's period) than for lower. It is the “rate of change” of the phase across frequencies that is determined by the conduction delay between the two oscillating signals. The gradient of a line fitted to the phase spectrum across frequencies after the phase has been divided by  $2\pi$  is equivalent to the conduction delay.

### 2.1.2 Wavelet derived estimates of power and coherence

In contrast to Fourier transforms, wavelet transforms are localised in both the frequency and time domains. Wavelet transforms provide a detailed representation of a signal in time and frequency with the principle drawback of being comparatively slow to perform. This is less relevant to the data analysed in this thesis since neural events occur on the millisecond to second time range. Therefore most of the analysis performed was using windows less than 2 seconds; the precise length being described in the relevant experimental chapter.

All wavelet analysis employed the Morlet wavelet function  $\psi_0(\eta)$  which has previously been used for both EEG, EMG and tremor analysis (Strambi et. al. 2004; Samar et. al., 1999). This wavelet can be defined mathematically in non-dimensional time  $\eta$  as:

$$\psi_0(\eta) = \pi^{-1/4} e^{i\omega_0\eta} e^{-\eta^2/2}, \quad (7)$$

which is a complex sine wave with Gaussian amplitude modulation. Variable  $i = \sqrt{-1}$  give this function both real and complex parts while  $\omega_0$  is the non-dimensional frequency used alongside  $\eta$  to satisfy the admissibility condition to be defined as a wavelet (Farge 1992). (This condition states that to be a wavelet the area under the function  $\psi_0(\eta)$  has to be equal to zero).  $\omega_0$  is of more than theoretical significance since it determines the time-frequency trade-off in a manner analogous to nFFT. In all analyses  $\omega_0 = 6$  since this provides a suitable compromise and has been applied previously for use with neural signals.

Conceptually the wavelet transform of a time series  $x_n$  in the time domain can be thought of as fitting a localized waveform of constant period to the signal at time  $n$  and sequentially shifting this along by equal time intervals until the frequency content at a single frequency is derived from all time points of interest. In the frequency domain, the wavelet's scale  $s$  defines the frequency of interest and this parameter can be changed to accommodate a bandwidth of interest and with a relative frequency resolution defined by

the interval between scales. This is more formally known as the Continuous Wavelet Transform,  $W_n(s)$  at scale  $s$ , and is defined as:

$$W_n(s) = \sum_{n'=0}^{N-1} x_{n'} \psi * \left[ \frac{(n'-n)}{s} \right] \quad (8)$$

Although it is possible to define a very small interval between scales or to sample at higher  $fs$ , below a certain level of scale interval or sampling interval additional frequency or time resolution cannot be gained since this is principally defined by  $\omega_0$ . In the analysis presented in this thesis each wavelet transform was performed on each sampling interval using specific scales and intervals between scales defined in each experimental chapter.

Rather than compute each transform from  $n = 1$  to  $N$  individually the method outlined in Torrance and Compo (1998) was used to improve the speed of transforms both on and off-line. To compute the  $N$  convolutions simultaneously the wavelet transform can be considered as the inverse Fourier transform of the product of the wavelet function in Fourier space ( $\hat{\psi}(s\omega_k)$ ) and the DFT of all  $N$  points:

$$W_n(s) = \sum_{k=0}^{N-1} \hat{x}_k \hat{\psi} * (s\omega_k) e^{i\omega_k n \delta t} \quad (9)$$

Where  $k = 0 \dots N-1$  and is the frequency index,  $\hat{x}_k$  is the DFT of  $x_n$ .



Since the Morlet wavelet transform produces a complex result wavelet power  $|W_n^y(s)|^2$ , the so-called “analytic” amplitude and phase can be readily derived. Relevant substitution of equation (1.12) derives wavelet coherence (Klein et. al., 2006).

$$Coh_n^{xy}(s) = \frac{\left| \sum_{t=1}^T W_n^{xy}(s) \right|^2}{\sum_{t=1}^T |W_n^x(s)|^2 \cdot \sum_{t=1}^T |W_n^y(s)|^2} \quad (10)$$

Here  $T$  is the number of trials.

### 2.1.3 Instantaneous phase and circular statistics

The instantaneous phase differs from the phase derived from the coherence spectra in that it is a true representation of a signal’s phase as it evolves in time. Algorithms such as the wavelet transform or Hilbert transform allow the amplitude and the phase of the waveform to be examined as separate entities. The instantaneous phase  $\phi_n$  can be derived either by taking the complex argument (or inverse tangent), of the angle formed by the real and imaginary products of these transforms. For example the phase at wavelet scale  $s$  at sample  $n$  is  $\phi_n(s) = \tan^{-1} \Im(W_n^x(s)) / \Re(W_n^x(s))$ . Simple statistical descriptions analogous to their linear counterparts can be calculated from whole populations of angles. The circular mean  $\hat{\mu}$  (mean angle) of angles at sample  $n$  and scale  $s$  across  $T$  trials is;

$$\hat{\mu}_n(s) = \tan^{-1} \frac{\sum_{t=1}^T \sin(\phi_{n,t}(s))}{\sum_{t=1}^T \cos(\phi_{n,t}(s))}, \quad (11)$$

and the circular dispersion  $\kappa$  (analogous to the variance of a linear distribution) is derived accordingly;

$$\kappa_n(s) = \frac{1}{T} \sum_{t=1}^T |\sin \phi_{n,t}(s) - \hat{\mu}_n(s)|. \quad (12)$$

Finally the distribution of angles at any particular sampled time point or wavelet scale can be tested against the null hypothesis of a von Mises distribution using the Rayleigh statistic of uniformity. The Rayleigh statistic for  $T$  angles at sample  $n$  and at wavelet scale  $s$ ;

$$\bar{R}_n(s) = \frac{\sqrt{\left(\sum_{t=1}^T (\cos \phi_{n,t}(s))^2\right) + \left(\sum_{t=1}^T (\sin \phi_{n,t}(s))^2\right)}}{N} \quad (13)$$

can be used in a manner analogous to the tests of a normal linear distribution such as the Kolmogorov-Smirnov test (Fisher, 1993).

## 2.2 Analogue online triggering.

The signal of interest (eg. EEG, microtremor) was amplified and prefiltered before being electronically processed by a custom built 16<sup>th</sup>-order elliptic 13-35 Hz bandpass filter. The filter had a stopband attenuation of 60 dB and an output delay of 50ms. After on-line rectification the signal was used to trigger a rising voltage threshold in a Schmitt circuit.

The voltage threshold was defined empirically to generate an output rate that approximately equalled the rate of occurrence of phasic oscillatory bursts.

## **2.3 Recordings.**

### **2.3.1 Electromyography (EMG).**

Surface EMG was recorded using pairs of 9 mm silver chloride electrodes applied to the belly of the appropriate muscle, and fastened with tape. Typically recordings were made from the first dorsal interosseous (FDI), extensor indicis (EI) and adductor digiti minimi (ADM). The skin was cleaned with alcohol prior to applying the electrodes and conducting jelly (Sigma, Parker Laboratories, New Jersey, USA) was applied to the base of the electrode to ensure a good contact between the skin surface and the electrode contact. The EMG was grounded to an electrode attached in a similar manner as above to the wrist.

### **2.3.2 Electroencephalography (EEG).**

EEG was recorded using 9 mm silver chloride electrodes attached to the scalp surface using collodion (SLE diagnostics, Surrey, UK). Typically electrodes were positioned either according to the international 10-20 placement system (Misulus, 1997) or 2cm in front of and behind the motor cortex hand area in the anterior-posterior plane. These

electrodes were amplified differentially with the most anterior electrode connected to the positive terminal and the posterior to the negative. Therefore positive deflections of the EEG represented an increase in voltage over the anterior electrode and negative deflections over the positive. The motor cortex hand area was determined by TMS. Prior to fixation, the scalp skin was cleaned with alcohol and conducting jelly (Sigma, Parker Laboratories, New Jersey, USA) was applied to the base of the electrode as for the EMG recordings. Both bipolar and monopolar signals were recorded online with the monopolar reference to an electrode attached to the earlobe with tape. Grounding of the EEG was achieved by an additional ground electrode on the forehead. In all cases reference and ground electrodes were attached using tape after cleaning the skin with alcohol.

### **2.3.3 Electrocorticography (EcoG).**

Local field potential (LFP) recordings were made in patients who had undergone functional neurosurgery for Parkinson's disease or chronic pain syndromes. Although the number of electrodes and the montage could vary between patients, the pain patients consistently had at least one electrode strip running across the central sulcus; overlying the pre- and post-central gyri, whereas the Parkinsonian patients had at least one strip running along the precentral gyrus. Each strip (Resume®; Medtronic, Minneapolis, USA) consisted of four 4mm contacts (0-3) with 1 cm distance between each contact.

Prior to intra-operative implantation of the electrodes fMRI was used to define the central sulcus and upper limb motor area. Under general anaesthesia a pair of burr-holes were formed for insertion of the electrode strip which were inserted into the extradural space.

The correct localization of the electrode was confirmed by bipolar cortical stimulation inducing evoked motor responses, with pulse trains of 5 to 10 shocks of 100- to 500-microsecond duration at 10 to 20 mA. Motor responses were monitored by EMG recording. The electrode was shifted slightly if necessary until the motor responses in the opposite hand were obtained.

In the pain patients studied, electrodes were typically implanted across the hand area of central sulcus. This was localized initially with fMRI for the burr-hole placement. The sensory cortex was functionally localized using the phase reversal method of Wood et. al.,1988. In this method, the responses to median nerve stimuli are recorded while the electrode strip is gradually manipulated to a region on the cortex where the response precentrally is of a positive (P20) polarity and the response post-centrally is of the opposite polarity. The region with the maximal negative deflection post-centrally is defined as the primary sensory hand area. In these patients the motor cortex was also located by stimulating through the contacts of the electrode strip using the same protocol described above.

#### **2.3.4 Accelerometry.**

Single axis accelerometers (EGAXT-50; Entran, Fairfield, USA) were used in this thesis to measure the acceleration profile of voluntary ballistic movements. This device consists of a suspended cantilever beam which is connected to a transistor which allows the acceleration profile to be represented as a simple analogue signal.

#### **2.3.5 Transcranial magnetic stimulation (TMS).**

In this thesis, TMS was used both for functional localisation of the hand area, for subsequent positioning of electrodes for EEG recordings, and in chapter 4 as a tool to test corticospinal excitability.

Current is produced in the brain by discharging a magnetic field (typically up to 3 Telsa) over a short time interval (1ms) (Rothwell, 1997). The precise mechanisms whereby this induced current produces a motor evoked response is uncertain. Recordings in monkeys suggest that the basic profile of the response to magnetic stimulation is similar to that of electrical stimulation. In these experiments single pyramidal tract neurons fired with a series of repetitive volleys at short (~ 1.5ms) intervals. The first of these is designated the direct wave since its latency was consistent with direct excitation of the neuron's proximal segment. Typically three later "indirect" waves are observed the origin of which is unknown. The principle difference between electrical and magnetic stimulation, is that

in the latter at low intensities still sufficient to evoke a motor response no D wave is seen (Edgley et. al, 1990).

In all the experiments using TMS magnetic stimuli were produced using a monophasic pulse generator (Magstim 200, Rochdale, UK) and delivered with a figure of eight coil to minimise current spread. The coil handle was oriented at  $45^{\circ}$  relative to the posterolateral planes.

### 2.3.6 Amplification, filtering and acquisition of signals.

Signals were all amplified with either a Digitimer D360 or Digitimer D160 (both Digitimer, Welwyn Garden City, UK) unless stated otherwise in the specific chapter. A-D conversion was achieved with 12 bit resolution using a 1401 (Cambridge Electronic Design, Cambridge, UK). Sampling rates are stated in the specific chapter. The following table summarises the amplification and filtering settings used for the different signals acquired in this thesis.

	<b>Amplification (x 10<sup>3</sup>)</b>	<b>Highpass (Hz)</b>	<b>Lowpass (Hz)</b>
<b>EMG</b>	1-2	16	300
<b>EEG</b>	5-50	1	100
<b>EcoG</b>	1-5	1	250
<b>Accelerometry</b>	None or 5	100	NA

**Table 2.1: Amplification and filtering settings.** NA = Not applicable. Filters were all first order butterworth.

The total band pass sensitivity of the amplifiers used was highpass 0.2Hz and lowpass 30000Hz. All signals were acquired online using a PC running either Spike2 v 5.06 or Signal v3 (CED, Cambridge, UK).



## **Chapter 3 : Premovement beta oscillations are associated with reduced acceleration of ballistic voluntary movements.**

Oscillatory activity in the beta range has been correlated with the symptoms of bradykinesia and rigidity in Parkinson's disease (see Introduction Chapter 1). One potential confound to the interpretation of this argument is that the dopamine depleted brain may produce epiphenomenal processes which are tightly correlated with the disease state but are not causative in their own right. In these experiments I test the hypothesis that the transient incidence of beta oscillations in the corticospinal tract of healthy subjects is associated with an impaired ability to produce rapid voluntary movements.

### **3.1 The amplitude of beta microtremor bursts is inversely correlated with the acceleration produced during a ballistic finger movement.**

#### **3.1.1 Introduction**

The aim of this study is to establish whether variations in the performance (the reaction time, acceleration) of a movement, can be explained by the effect of fluctuations in the degree of beta oscillatory activity. In these experiments I correlate these performance fluctuations with the amplitude of beta oscillations from two sources; the scalp EEG and the microtremor recorded peripherally, in an attempt to establish whether any direct relationship exists on a single trial basis. In contrast to the EEG, where correlations were difficult to reproduce across subjects, the peripheral signal consistently negatively

correlated with the acceleration of the movement. Evidence in the form of consistent cortico-acclerometer coherence argues that this results at least in part, from the cortical drive to muscle at beta frequencies.

### **3.1.2 Methods.**

#### *Subjects*

Twelve healthy subjects, four female (aged between 22 and 35 years) all right handed participated.

#### *Paradigm*

Subjects were comfortably seated with their forearms supported on a table. The experiment was designed to investigate the effect of cortically projected oscillatory activity on the dynamic features of muscle contraction (reaction time, acceleration) when making the transition from a postural context to a simple phasic movement. This was implemented by asking the subject to maintain a tonic postural contraction by holding their index fingers in both right and left hands at a comfortable level of contraction. On presentation of a LED cue subjects were instructed to immediately abduct their right index finger while maintaining the hold position in their left. Emphasis was placed on producing a consistently fast reaction time. The cue was presented for 150ms at pseudo-randomised time intervals between 5.1 and 30 seconds using an automated randomising

device (D4030 pulse generator, Digitimer, Welwyn Garden City, UK). To prevent muscle fatigue or extreme fluctuations in attention that might confound the results, movements were recorded across four ten minute blocks. A total of between 120-140 movements were accumulated during each recording.

### *Recordings*

Accelerometers have previously been used in studies of physiological tremor since they are particularly sensitive to the mechanical effect that motor unit synchronization has on the joint that the muscle acts upon. With this in mind, accelerometers (EGAXT-50; Entran, Fairfield, USA) were attached to the medial aspects of the tip of the extended left and right index fingers in the plane of the movement. In addition, surface EMG was recorded from FDI and EI using bipolar 9mm silver nickel electrodes referenced to an electrode on the styloid process. The muscle belly of EI was detected through palpating at a point on the arm close to its proximal origin while the subject repeatedly extended their index finger.

Transcranial magnetic stimulator (Magstim 200, Rochdale, UK.) was used to locate the motor cortex hand area so that a Laplacian EEG configuration could be recorded from as local a site as possible. The hand area “hotspot” was defined as the site of stimulation at which TMS evoked the most consistent motor evoked potential (MEP) at the lowest stimulus intensity in the FDI muscle. Active motor threshold was determined by identifying the minimum stimulus intensity required to elicit at least five out of ten MEPs

with an amplitude of 0.2 mV. Once established the intensity of stimulation was progressively reduced until the most focal cortical representation of FDI was found. Four 9mm silver-nickel electrodes were then positioned on the scalp around a central “hotspot” electrode, each 2.5cm from the central electrode and at ninety degrees to each other. All were referenced to an electrode on the contralateral ear.

Offline analysis required the comparison of how the peak acceleration varied with the degree of oscillatory activity in the beta bandwidth. To improve the signal to noise ratio both the left and right accelerometers were amplified. The right was also collected without amplification to prevent saturation of the peak acceleration (PA) produced for each movement.

Filtering and gain settings are as specified in the chapter 2. Signals were sampled at 1000Hz for A-D conversion using a 1401 interface.

### *Analysis*

Regression analysis correlating the degree of beta synchronisation and the PA or RT for each individual movement was performed by extracting the area under the squared, bandpassed filtered accelerometer signal and EEG electrodes. By extracting the area as a marker of beta synchrony at four 50ms epochs prior to cue presentation and at three epochs during cue presentation and correlating this with the PA or RT for the movement,

a direct relationship between the dynamic parameter and the short term synchrony of beta oscillations could be achieved.

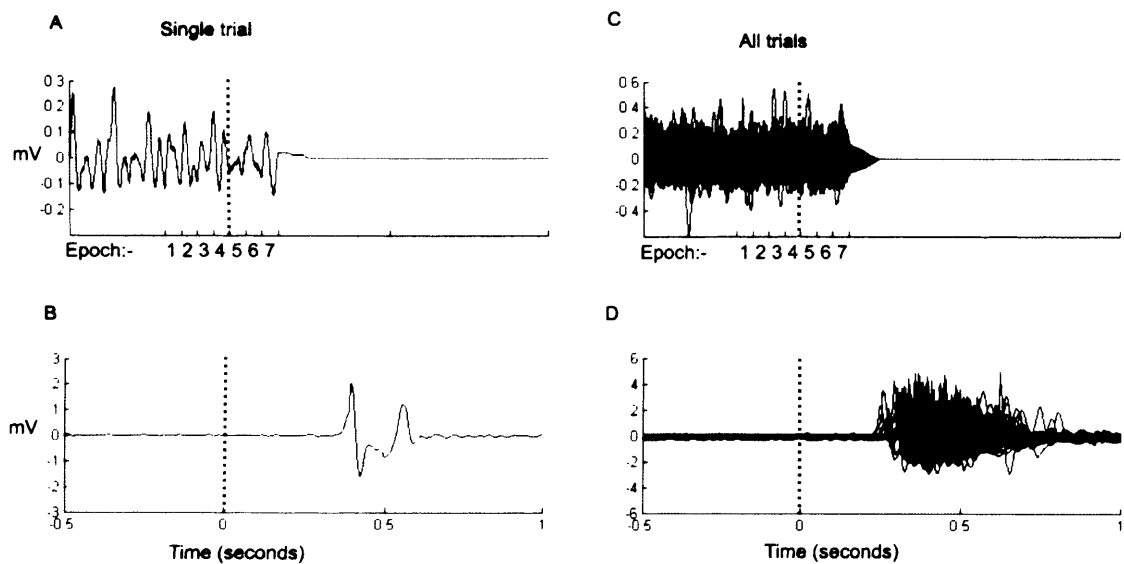
At high gain the accelerometer becomes sensitive to minor jerks unrelated to the task that would otherwise confound the results; hence any area values that were outwith three standard deviations of the mean were removed from the analysis. Visual inspection of the trace demonstrated that this was a reliable method for including oscillatory activity related solely to spontaneous changes in the patterns of motor unit synchrony. Movements with scalp EMG or blink artifacts were rejected from the analysis of the EEG signal.

Any trials with a RT or triggering acceleration out with  $3 \times \text{SD}$  of the respective mean were rejected to limit artifacts due to very long reaction times and small shifts in the position of the finger, which nevertheless were associated with large accelerations leading to spurious triggering. Trials in which such a shift triggered the cue were distinguishable from genuine microtremor bursts since the former consisted of abrupt non-oscillatory deflections in the raw acceleration trace that were considerably larger in amplitude than the background activity.

The bandpass frequency for analysis was determined by inspection of the individual's power spectrum. In most of the subjects a prominent peak between 13-30Hz was seen in the accelerometer trace, as shown previously (Halliday et. al., 1999) whereas the EEG signal contained less lower frequency activity, here a bandpass of 22-30Hz was most

commonly used. All filtering was performed in Spike v 5.16 (CED, Cambridge, UK) using the Finite impulse response algorithms included in this software. These bandpass parameters were further justified by the results of coherence analysis (see results) where cortico-muscular coherence demonstrated that on average, these were the most prominent frequencies.

One potential danger of correlating the filtered premovement microtremor with the movement performance on each trial is that the movement itself, due to the temporal properties of the filtering, could become spuriously included in the analysis windows. To avoid this confound the accelerometer trace was padded with zeros from 150ms after cue presentation for 1 second. This procedure was as performed before filtering and is illustrated in figure 3.1.1.



**Figure 3.1.1 Analysis of accelerometry.** (A and B) Single trial microtremor and movement accelerometry profiles. The movement profile is removed

prior to filtering to reduce the potential contamination of the microtremor by the acceleration profile of the movement. Note in pannel D that movement profiles in this subject are eliminated from the microtremor traces overlaid in C by this proceedure. The red dotted line in each pannel represents the cue onset.

To confirm that the beta synchronisation recorded in the accelerometer signal was of cortical origin, coherence analysis was performed between the Transformed EEG (Horth et. al, 2001) and the microtremor (see chapter 2 for details). A segment length of 1024 points was used with a frequency resolution of 1.13Hz. Values of coherence and phase for each frequency up to 80 Hz were established by averaging over a mean of 558 (range 491-612) segments. Segments all consisted of intercue non-movement periods to prevent movement artifacts from undermining accurate coherence estimation. The Bonferonni corrected Z-score (mean / SE; according to Roelfselma et. al, 1997) of the coherence across subjects was deemed significant at the 95% CL, where  $p < 0.0006$  (corrected for 74 frequencies ) and Z was  $> 3.2$ .

In all analyses across subjects correlation coefficients or coherence values were Fisher transformed before averaging.

The conduction delay was calculated from the cortico-accelerometer coherence by fitting a slope to the phase over frequencies with significant coherence.

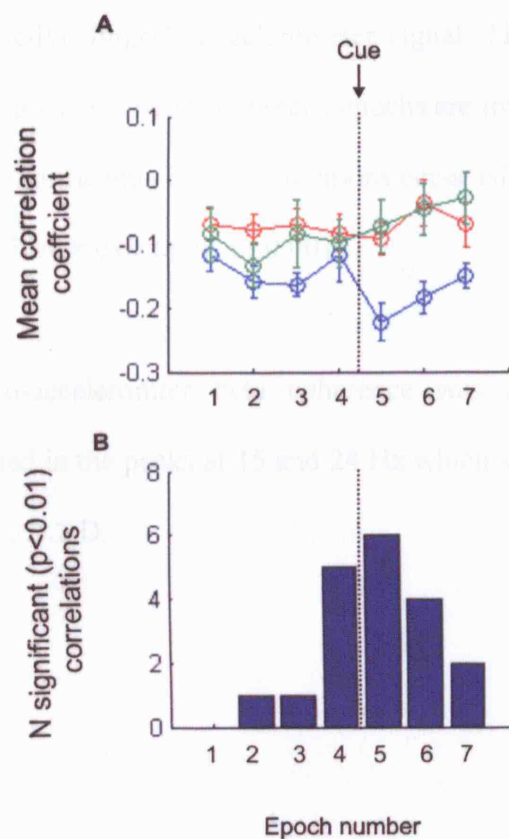
### 3.1.3 Results:

After artifact rejection a total of over 1500 finger movements were analyzed for the twelve subjects (individual range 117-143, mean  $133 \pm 7$ ), with an average reaction time of  $306 \pm 7$  ms. No significant correlations were found in any of the subjects between the RT and the degree of beta synchronization in the EEG signal or the accelerometer. In contrast, PA was correlated with the beta activity in the accelerometer signal within 95% confidence levels in 10 of the 12 subjects and with 99% confidence in 7 of the subjects. The EEG signal was less informative; from only three of the subjects could a correlation with 95% confidence be made. All of the correlations established a negative relationship between beta oscillatory activity and peak acceleration whereby large bursts of activity were associated with low levels of PA and the highest levels were associated with little or no beta synchronization.

The average strength of the correlation (the  $r$  value) for the twelve subjects is plotted in figure 3.1.1 (A). On average, the strength of the correlation for the twelve subjects is strongest at the time of cue presentation in the right hand. A repeated measure ANOVA with factors “signal” (right pass band, left pass band, right stop band) and “time” (epochs 1-7) demonstrated a significant effect of signal ( $F(1,11) = 5.8$ ,  $P = 0.01$ ) but no interaction between the two factors ( $F(1,11) = 1.2$ ,  $P = 0.2$ ) or effect of time ( $F(1,11) = 1.8$ ,  $P = 0.1$ ). Post-hoc differences in the mean correlation strength existed between the beta band pass signal in the right and left accelerometer signals ( $p = 0.005$ ) and the band pass



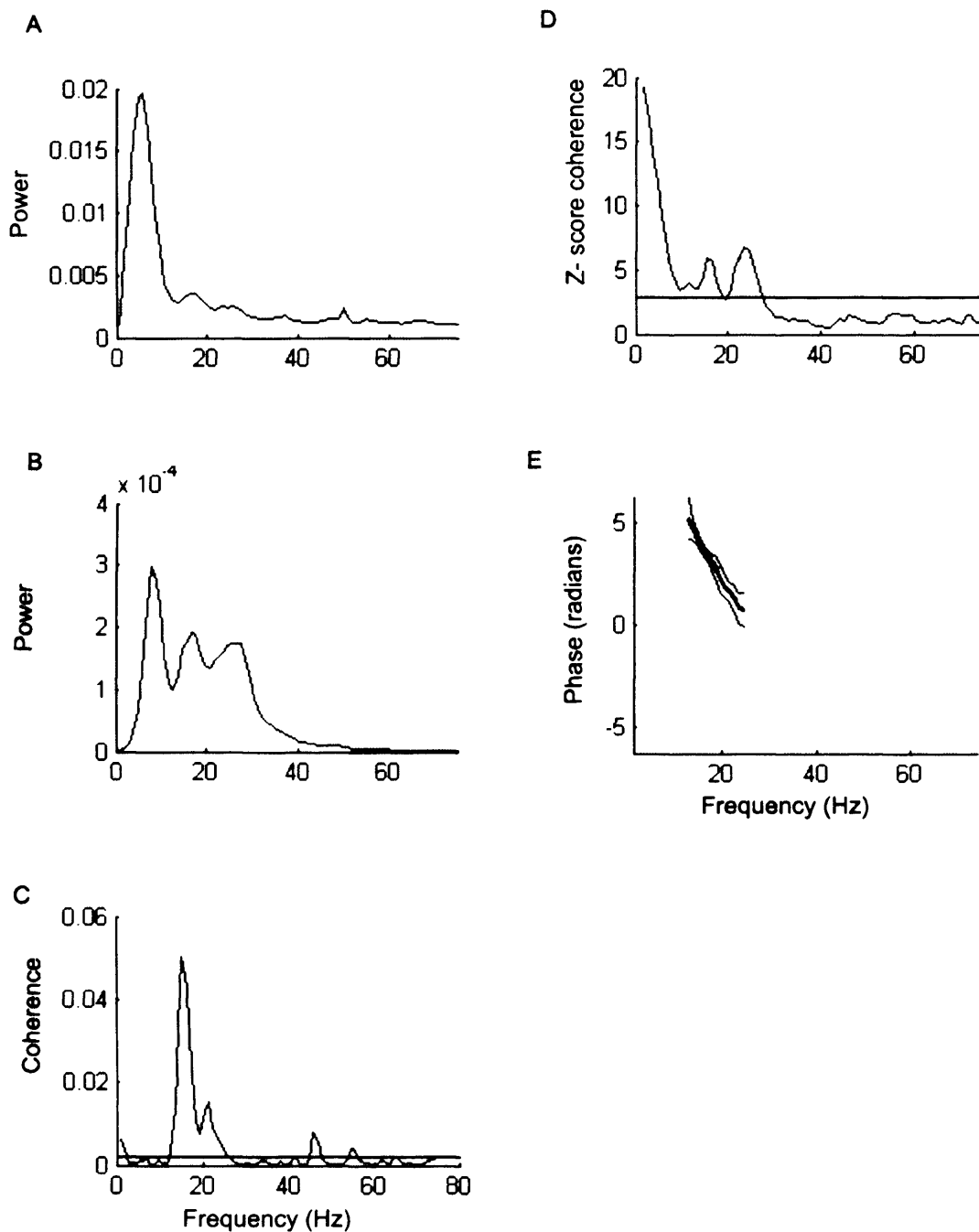
and band stop accelerometer signals recorded from the right ( $p = 0.02$ ). Non-parametric evaluation of the number of predictions within the three epochs prior to cue and the remaining four epochs illustrated a significant difference between the two time periods for predictions made with 99% confidence (Fisher exact test  $p < 0.001$ ), figure 3.1.1 (B). These results suggested that the relationship was lateralised, and that there was a tendency for these correlations to occur prior to a movement, but with little temporal specificity between subjects.



**Figure 3.1.2 Parametric and non-parametric analysis of correlations between microtremor beta activity and PA.** The mean  $\pm$  SEM correlation coefficient between the trial to trial fluctuations in beta amplitude and movement acceleration are plotted in (A). The blue line represents the mean  $r$

values at each epoch across the 12 subjects when the microtremor signal was bandpass filtered in the beta range. The red line represents correlations from the bandpass filtered signal from the contralateral finger microtremor (non-active) and the green line is the correlations derived after band stop filtering the beta range microtremor from the ipsilateral (active) finger. (B) The number of significant correlations are plotted as a function of the 50ms analysis epochs for correlations derived from the bandpass filtering of the active finger's accelerometer signal. The cue was presented at the start of epoch 5. Therefore precue epochs are from 1-4 and post cue epochs from 5-7. Significantly more correlations occurred within epochs 4-6 than in epochs 1-3 (Fisher exact test,  $p < 0.001$ ).

Cortico-accelerometer beta coherence was consistently present across the subjects, reflected in the peaks at 15 and 24 Hz which surpass the Z-score 95% confidence limit in figure 3.1.2 D.



**Figure 3.1.3 Cortico-accelerometer coherence in a single subject and across the subject population.** (A) Example of EEG and accelerometer power (B) and coherence between EEG and accelerometer in a single subject (C). Conduction delay estimate from the phase in this subject was 15ms (E).

Z-transformed coherence across the subject population in (D). The horizontal line represents the 95% confidence limit.

#### **3.1.4. Discussion.**

In this experiment I have demonstrated that large amplitude beta oscillations in the microtremor of healthy subjects are associated with impaired generation of ballistic force. Why might the microtremor, which is the mechanical product of motor unit synchronization (Halliday, 1999), provide a better index of this relationship than the scalp EEG? One explanation is that this relationship is not mediated by oscillatory activity in the cortex, but is rather the exclusive consequence of alterations in the properties of lower motoneurons, and is therefore best indexed by a peripherally generated signal. This possibility is made likely by the fact that oscillations at beta frequencies can be produced without cortical (Norton et. al., 2004) input to muscle. Furthermore, neuronal processing in the spinal cord contributes to the shaping of the motor output (Prut and Fetz, 1999) and may be a potential site for intrinsically generated oscillations to impede the motor performance seen here. These are feasible possibilities, however, the exclusivity of this effect would be unlikely because oscillations in this frequency band are inextricably linked with the cortex, as indexed by the cortico-accelerometer coherence seen in this study. In other words, it is unlikely that cortical oscillations do not contribute at least in part to this relationship, even if the cortex is not the site of a “recruitment impairment”. The most likely reason for the lack of correlations seen when the EEG was used as the correlating signal would be the comparatively poorer SNR and spatial resolution. This

assumes that beta activity within the motor cortex shows spatial definition. In the recordings I have made from ECOG electrodes in M1 the beta ECOG can be very different in character between contacts separated by 1cm. Indeed this spatial non-uniformity was also remarked upon by Penfield and Jasper (1949), in their original recordings of M1 oscillatory activity. The microtremor may therefore provide a spatially resolved view onto the descending drive from a set of corticospinal neurons associated with related muscle fields.

The properties of motor unit firing and recruitment have been studied in the human hand and leg muscles. Two specific differences exist between slow and ballistic movements. Firstly, in contrast to slow movements, where a gradual increase in motor unit firing rate is seen, the increase in rate at the onset of a ballistic contraction is of a short duration and is explosive in its onset, firing rates of up to 120 Hz have been reported (Desmedt and Godaux, 1977b; 1978). Secondly the feature that allows this rate to be achieved is the reduction in the threshold of high threshold motor units, allowing these units to be recruited at lower levels of force, and presumably lower levels of synaptic input (Desmet and Gadaux, 1977a). The results of this study would argue that at some point the processes that promote this high firing rate, and hence rapid change in force (acceleration), must be compromised by the incidence of a large amplitude beta oscillation. The question is, why?

Recently, Van Cutsem and Duchateau (2005) have demonstrated that the acceleration of a movement produced from rest is consistently larger than that produced when the

movements are superimposed on ongoing postural EMG. These authors argued that the ability to produce a short EMG silent period prior to the movement predicted the eventual ballistic force of the movement. Movements without a silent period were associated with a longer first ISI at the onset of the ballistic movement reducing its acceleration. Premovement silent periods were not observed prior to these finger movements, nevertheless, could the results presented here be a simple function of fluctuations in the background level of EMG? If this were the case then a similar relationship should have occurred between the acceleration and the beta band stop filtered accelerometer signal, however these correlations were significantly smaller from those seen using the bandpass filtered beta microtremor. It would seem therefore that something specific to rhythmic muscle synchronization at beta frequencies is associated with impaired ballistic force production. If prior muscle activity is detrimental to effective ballistic motor unit recruitment then a history of oscillatory muscle activity may produce an additional detriment over and above that seen when the muscle is active but desynchronized.

### **3.2. Ballistic motor performance is degraded by premovement beta oscillations**

#### **3.2.1 Introduction**

In the experiments described in section 3.1, there was considerable variability between subjects in terms of the time course of the correlation between the beta microtremor amplitude and the movement's acceleration. This prevented me from concluding that any specific time point was important for the expression of this relationship. Such a non-

specificity in time could be due to differences between subjects, it could also be due to the inherent stochasticity of the oscillations mediating the effect. In the experiments I present below, the aim was to produce an artificial stationarity to these oscillations in an attempt to argue that, within a specific window of opportunity this state can degrade motor performance of ballistic movements. In other words, the aim was to slow the movements of healthy subjects by biasing the timing of voluntary movements to coincide with stochastic oscillatory events.

### **3.2.2 Methods**

#### *Subjects*

Ten right-handed healthy subjects (mean age 29 yrs, range 22 - 35 yrs, two females) participated.

#### *Paradigm*

The first prediction I sought to test was that movements triggered during periods of elevated beta frequency band synchrony amongst relevant cortical neurons would be slowed in healthy subjects. I developed a simple visually cued reaction time paradigm in which the time of the cue's presentation was determined by the stochastic incidence of a microtremor oscillation. Subjects were instructed to abduct their extended right index finger  $\geq 10^\circ$  as quickly as possible on illumination of a light emitting diode, and the speeds of these "triggered" movements were compared to those performed when the

same cue was presented at random time intervals during the same recording session. Both Triggered (TC) and Random (RC) cues were delivered at a minimum interval of 5 seconds with RC presentation determined by a pseudo-randomised output device (D4030 pulse generator, Digitimer, Welwyn Garden City, UK) with a maximum interval of 30 seconds.

Subjects were seated with their forearms supported on a table with both their right and left index fingers abducted slightly and tonically extended against gravity. Finger microtremor was detected by accelerometers (EGAXT-50; Entran, Fairfield, USA) attached to the medial aspect of the distal phalanx of the right and left index finger. The analogue triggering algorithm described in chapter 2 was used to “trigger” the cue. Thus the TC was presented 50 ms after the onset of phasic increases in beta frequency band microtremor once the delay in the filter had been taken into account. The threshold was adjusted to allow an approximately equal number of TC to RC during each session. Four or five recording sessions of 2-4 minute runs, separated by 1-2 minutes rest, were performed over a 30-minute period after a practice session of 3-5 minutes.

### *Recording*

In addition to the accelerometry, EMG was recorded from the first dorsal interosseous (FDI), and extensor indicis (EI) using 9mm silver-silver chloride electrodes in a bipolar montage. Signals were amplified and filtered according to the settings in chapter 2. All signals were acquired with a sampling rate of 1000Hz.



## *Analysis*

The extraction of the movement variables, Reaction Time (RT) and Peak Acceleration (PA), was implemented off-line in Spike. RT was determined by measuring the time between cue onset and the start of the acceleration accompanying movement. PA was defined as the maximal acceleration in the direction of the voluntary movement within 100ms of the initial acceleration point that defined the RT. This window was sufficient to capture the major deflection in the accelerometer trace. Any trials with a RT or triggering acceleration out with 3 x SD of the respective mean were rejected to limit artifacts due to very long reaction times and small shifts in the position of the finger, which nevertheless were associated with large accelerations leading to spurious triggering. Trials in which such a shift triggered the cue were distinguishable from genuine microtremor bursts since the former consisted of abrupt non-oscillatory deflections in the raw acceleration trace that were considerably larger in amplitude than the background activity. An average of  $89 \pm 7$  triggered cue (TC) and  $57 \pm 4$  randomly cued (RC) trials were analyzed in the 10 subjects after a median of 10% of trials were rejected.

Finger tremor in the beta frequency band has been considered to be the mechanical product of synchronization of motor unit activity within and between muscles, which itself is due to synchronization within the beta activity in the corticospinal system (Halliday et al., 1999; McAuley et al., 1997). To confirm that periods of elevated beta band microtremor were accompanied by increased descending drive at similar frequencies in our paradigm we derived a measure of short-term synchronization between

the two muscles involved in the task, FDI and EI, using a wavelet based approach (see chapter 2 for details). A value for intermuscular synchrony was derived by cross-correlating the wavelet decomposed EMG activity at the Peak Trigger Frequency (PTF) during the triggered trials. This frequency was found after averaging the CWT of the accelerometer signal 0.4 seconds prior to the cue and 0.1 seconds post cue presentation. Wavelet coefficients were extracted at a time resolution of 1ms and at scales corresponding to frequencies between 11 and 39 Hz, with a resolution of 0.4 Hz. To prevent amplitude cancellation due to averaging over trials with phase differences relative to the trigger stimulus all coefficients were converted to wavelet power. The CWT of the two EMG signals at the PTF were cross-correlated over a 0.4 second precue and 0.1 second postcue period using a 128 ms overlapping sliding window shifted by 1ms. The cross correlation coefficients were then averaged across the random or the triggered trials and a peak value was extracted from each average within a window defined between 50ms prior to the cue (allowing for the filter delay) and one cycle of the PTF. All values were normalized using the Fisher transform.

To determine the duration of bursts of beta frequency band microtremor the wavelet power at the PTF was averaged around each time point at which power first exceeded the 95 % confidence limit of background power.

One potential confound in the interpretation of these experiments is that the peripheral manifestation of the oscillations in muscle is to produce a refractory state which prevents effective fusion of the muscle fibers. I tested the possibility that a change in the properties

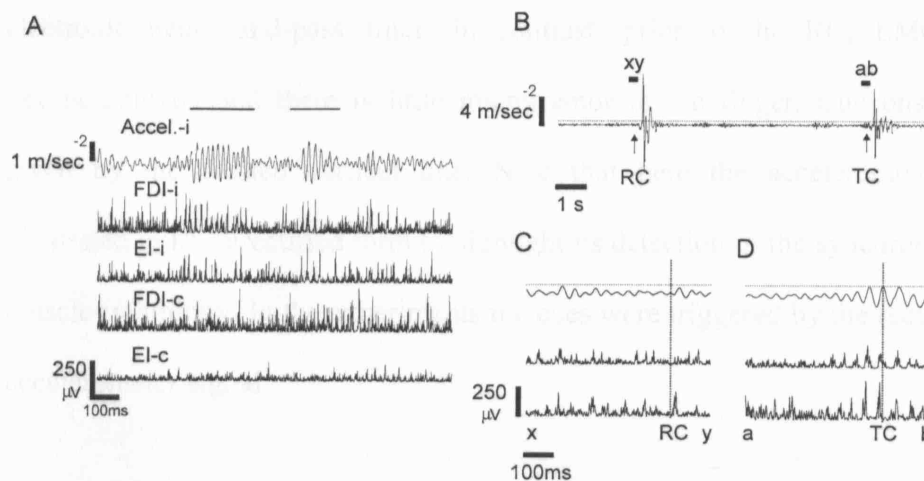
of the muscle contractile apparatus had occurred by stimulating the muscle directly when twitches were evoked by beta oscillations or at random intervals independently of the microtremor.

Stimulation (Devices Stimulator Type 3073) was delivered through two 9mm silver-silver chloride surface electrodes, one fixed over the motor point of FDI and one over the proximal interphalangeal joint of the tonically extended index finger. Shocks were square wave pulses of 0.2 ms duration of sufficient intensity to elicit twitches causing peak accelerations of the index finger that matched those seen in the reaction time experiments. Shocks were triggered by beta microtremor or delivered randomly in section 3.2, although an additional 285ms delay was added to the timings of each shock so that they were delivered at a time that corresponded to the average reaction time in the standard cued paradigm.

### **3.2.3 Results**

Ten healthy subjects held their index finger tonically extended and were instructed to abduct this finger as quickly as possible in response to a visual cue. The acceleration signal from the tonically extended index finger revealed phasic bursts of microtremor in the beta frequency (13-35 Hz) band between reaction time movements. Such microtremor bursts were associated with a series of simultaneous electromyogram (EMG) discharges in the first dorsal interosseous (FDI) and extensor indicis (EI) muscles repeating at intervals of about 50 ms (Figure. 3.2.1), and were used to trigger the visual stimulus after a 50 ms delay imposed by the use of an on-line electronic beta frequency band triggering

device. Note that microtremor bursts were prolonged (Figure. 3.2.1 (A)) and continued beyond the triggering oscillation in triggered trials (Figure. 3.2.1 (D)). Across the 10 healthy subjects microtremor bursts exceeding the 95% confidence limit (CL) of the mean power in the beta frequency band occurred every  $2.7 \pm 0.3$  seconds, exceeding this level for  $1.65 \pm 0.03$  cycles of the Peak Trigger Frequency (PTF) with a mean maximum duration of  $3.4 \pm 0.26$  PTF cycles. As bursts only exceeded 95% CL of the mean power near their peaks, these represent conservative estimates of microtremor burst duration.



**Figure 3.2.1. Beta frequency band microtremor in a single healthy**

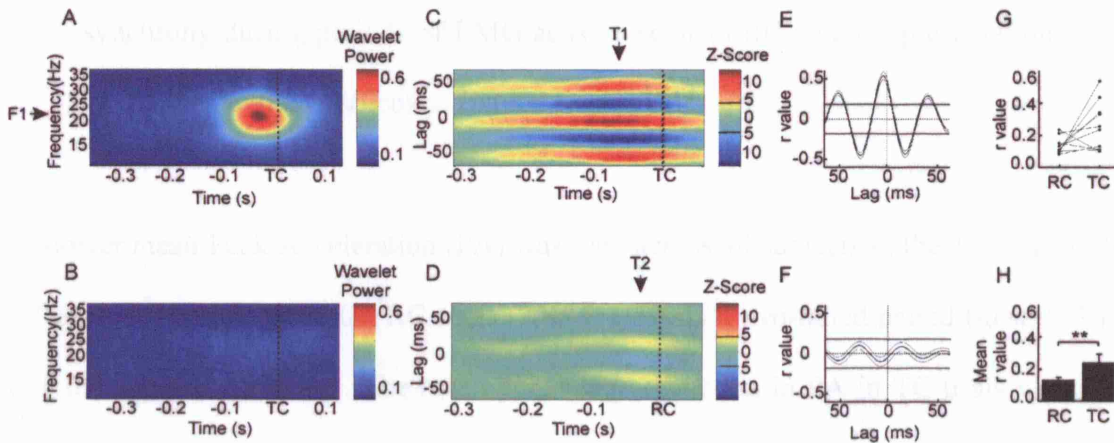
**subject.** (A), Spontaneous inter-trial microtremor and EMG from both ipsilateral and contralateral Extensor Indicis (EI) and First Dorsal interosseous (FDI) showing lateralised bursts of microtremor (marked by horizontal bars).

(B), Finger acceleration in response to cues. The first movement was made in response to a visual cue presented at random (RC). The second was made in response to a cue triggered by a transient increase in the beta band microtremor (TC). The thin horizontal line represents the voltage threshold for triggering the cue (triggering was only possible  $> 5$  s after the last

movement). (C), and (D), Acceleration, FDI and EI EMG during the periods between XY and AB for the RC and TC trial, respectively. Note the emergence of EMG bursts with an approximately 50ms period that are synchronized between the two muscles prior to the triggered cue. This synchronized EMG activity is reflected in the accelerometer signal. Cue presentation occurred 50 ms after beta microtremor exceeded trigger levels (thin horizontal lines), with this delay being determined by the on-line electronic beta band-pass filter. In contrast, prior to the RC, EMG is desynchronized and there is little microtremor in the finger. Cue onset is given by the dashed vertical line. Note that here the accelerometer is illustrated in its unrectified form to highlight its detection of the synchronized muscle rhythmicity. In the experiments the cues were triggered by the rectified accelerometer signal.

Correct triggering from periods of high beta band microtremor in Triggered Cue (TC) trials was confirmed by averaging the acceleration wavelet power around the cue period in each subject (Figure. 3.2.1 (A,B)). The mean PTF across subjects was  $25 \pm 0.9$  Hz. The hypothesis that periods of high beta band microtremor were due to phasic increases in corticospinal synchrony in the beta frequency band was supported by a simultaneously elevated intermuscular synchrony at the PTF in TC but not Random Cue (RC) trials (Figure. 3.2.2 (C-F)). This phasic increase in intermuscular synchrony at the time of triggering in TC trials was unilateral and involved periods of about 50 ms, consistent with synchronization between motor units at about 20 Hz (Figure. 3.2.2 (C)). Overall, the peak cross-correlation coefficient was higher in TC compared to RC trials across subjects

( $0.25 \pm 0.05$  and  $0.13 \pm 0.02$ , Wilcoxon Signed Ranks test,  $Z=1.98$ ,  $p=0.04$ : Figure. 3.2.2 (G-H)).

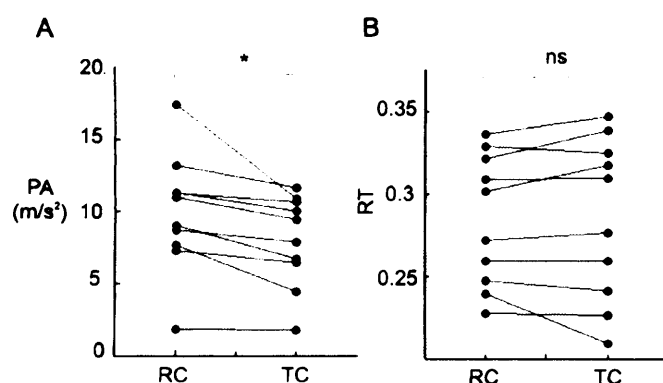


**Figure 3.2.2. Intermuscular synchrony in a single healthy subject.** Peak Acceleration (PA) was 18% less on average when cues were triggered ( $n=146$  movements) rather than randomly ( $n=72$ ) presented. (A, B) Wavelet transformed microtremor power averaged around triggered (TC) and random (RC) cues, respectively. (C,D) Averaged, time evolved cross correlation function between ipsilateral FDI and EI EMG at Peak Trigger Frequency (PTF) (21Hz, F1) in TC and RC trials. (E, F) Two dimensional cross correlations (thick lines) at maxima in C and D at T1 and T2, respectively, with respective SEMs (thin lines). 95% confidence limits are illustrated by the black horizontal lines on both the colour plot scales and the two dimensional correlations. Correlations with a Z score  $>4.75$  were considered significant (level determined after correction for multiple comparisons [129 lag points, 384 time points] by the Bonferroni method [see Roelfsema et al.

1997 for previous use of this technique]. This significance level was further verified using a shift control correlation where no correlations were above this level). (G, H), Individual and mean (+SEM) peak intermuscular synchrony during periods of EMG activity prior to RC and TC presentation.

\*\* denotes  $p=0.04$ , Wilcoxon Signed Ranks Test.

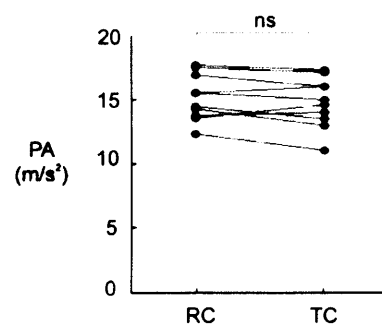
A slower mean Peak Acceleration (PA) was seen across all subjects in the TC trials ( $7.96 \pm 0.99 \text{ ms}^{-2}$ ) compared to the RC trials ( $9.85 \pm 1.29 \text{ ms}^{-2}$ , two-tailed paired t-test;  $t=3.19$ ,  $p=0.01$ : Figure. 3.2.3 (A)). The mean percentage reduction in PA in TC trials was  $19 \pm 4.6\%$  (range 4-40%). Thus elevations of beta activity several hundred ms prior to a motor response exerted a measurable effect upon movement execution, with the interval between onset of oscillatory bursts and response being determined by the reaction time (RT) plus the 50 ms delay imposed by the online beta filter in these experiments. There was no difference in RT between trial types ( $284 \pm 14\text{ms}$  in RC trials and  $285 \pm 17\text{ms}$  in TC trials; two-tailed paired t-test;  $t(9)= -0.16$ ,  $p=0.87$ : Figure. 3.2.1 (B)).



**Figure 3.2.3. Behavioral data for both triggered (TC) and randomly (RC) presented cues in 10 healthy subjects. (B), Individual mean Peak**

Acceleration (PA). \* denotes  $p=0.01$ , Wilcoxon Signed Ranks Test. (B), Individual mean Reaction Time (RT). ns=not significant ( $p=0.74$ ).

In the ancillary experiment in which muscle twitches were elicited by direct electrical stimulation the PA was measured in an average of  $86\pm6$  triggered and  $63\pm7$  random shocks in each of the 10 healthy subjects.



**Figure 3.2.4. Response to direct electrical stimulation of FDI.** Shocks were either delivered triggered (TC) by bursts of beta frequency band microtremor or presented randomly (RC) in 10 healthy subjects. Individual mean peak acceleration (PA) in elicited twitches. ns=not significant ( $p=0.14$ ).

Finger acceleration driven by direct stimulation of the muscle did not differ, whether shocks were delivered following bursts of beta band microtremor ( $14.76\pm0.61 \text{ ms}^{-2}$ ) or at random intervals ( $15.15\pm0.57$ , two-tailed paired t-test;  $t(9)=1.60$ ,  $p=0.14$ : Figure 3.2.4).

### 3.2.4. Discussion.

By biasing the timing of voluntary movements to be initiated after a transient period of beta synchronization, the ballistic performance of movements made by the healthy



subjects in this study could be consistently undermined. The bursts of beta microtremor used to trigger the cues to move were associated with synchronized EMG bursts between the active muscles at beta frequencies, indicative of a common cortical drive (Kilner et. al., 1999). Furthermore, an effect of beta oscillations on the mechanical properties of muscle was ruled out by the ancillary experiments. Specifically, these results extend those of the previous section (3.1) to argue that a cortically driven beta oscillation occurring (on average) ~350 ms prior to the initiation of a movement can undermine a movement's successful execution (at least in terms of the ballistic acceleration produced). This result would be inconsistent with a direct negative influence (for example "clamping the firing rate" [Murphy and Fetz, 1996b]) upon the coding functions of corticospinal neurons, since, even at their maximum average duration (3.5 cycles), the oscillations would be over by the time that effective rate coding starts (Evarts, 1968, 1974; Matsumara, 1979). A further argument against the idea that the oscillation is interacting with the neural processing at the time of movement execution is that the number of correlations seen in the experiments of section 3.1 did not simply ramp up as the movement approached. Collectively therefore, the balance of evidence from these two experiments would suggest that conflict at the level of *preparing* for rather than executing the movement is introduced by oscillatory activity within the corticospinal tract.

It is important to reiterate here that despite microtremor being associated with enhanced intermuscular synchrony, this index does not rule out the possibility that these results are the consequence of a spinal source of beta oscillations (Norton et. al. 2004), or the

intrinsic properties of lower motoneurons (Moritz et. al., 2005) to synchronise at beta frequencies. An interesting control experiment to establish whether changes in spinal excitability could be producing the result observed here would be to assess the size of the Hoffmann (H-reflex) reflex during microtremor bursts. This would provide critical evidence for the spinal or cortical origin of the ballistic force impairment seen here.

These results could be explained in terms of a neural state in which changes from one motor context to another is somehow impaired. Beta oscillations may be the trademark feature of a specific motor set which in these experiments is inappropriate “noise” caught up in the transition to a new set. This is not to say that the oscillation is noise in its appropriate setting, but rather that there are some inherent limitations in the neural machinery during transitions between motor sets. In the final chapter I will expand further upon the hypothetical basis of these limitations.

### **3.3 The amplitude of beta oscillations in the cortical ECOG is inversely correlated with the acceleration produced during a ballistic finger movement.**

#### **3.3.1. Introduction**

The experiments described up until now have not provided any evidence to say that the effect of beta oscillations during the preparatory period is on cortical neurons specifically. Although I have argued that the cortico-accelerometer and intermuscular coherence provide a “window” onto the pyramidal output neuron activity, a very feasible

argument is that although the oscillations may arise in the cortex and descend to the lower motoneuron pool, it is their effect upon these neurons that is manifest in the reduced acceleration of the movements. In section 3.1, the beta oscillations recorded from the scalp were poorly correlated with the eventual movement performance, here I utilize the high spatial resolution of intracortical ECOG recordings to test for a cortical correlate of the effects of beta oscillations on movement performance.

### **3.3.2 Methods.**

#### *Patients*

Recordings were made from two patients who had received functional neurosurgery for treatment of chronic pain. ECOG was recorded from epidural electrode strips implanted over the sensorimotor cortex. The electrode strips (Resume® Medtronic, Minneapolis, USA) consisted of four contacts (0-3) of 4 mm in diameter, each separated by 1 cm. In Patient *DF*, a 57-year old male with a 7 year history of Multiple Sclerosis and right sided Trigeminal Neuralgia a single strip was implanted across the central sulcus. The N20 component of the cortical potential evoked by intra-operative electrical stimulation of the contralateral median nerve at the wrist underwent polarity reversal at contact 1. This, together with the low threshold motor response to intra-operative direct electrical stimulation, confirmed that the most anterior contacts, 2 and 3, overlay the motor cortex. Patient *DF* was recorded 6 days post-operatively, while off medication. In subject *CO*, a 54-year old female with a 3 month history of left sided upper limb pain following basal

ganglia stroke two electrode strips were implanted parallel to and on either side of the right central sulcus. In the posterior electrode strip the N20 response was largest over contacts 1 and 2 while stimulation over contacts 0 and 1 of the anterior electrode strip elicited the largest MEP in Abductor Pollicis Brevis. Patient CO was recorded 1 day post- operatively while on medication (Daily dosage; Clonazepam 1mg, Gabapentin 800 mg and Ox-carbamazepine 300mg).

### *Paradigm*

The same reaction time paradigm used in section 3.1 was used. Here the timing of the cues was determined manually since recordings were made at the bedside. Patient CO was unable to produce comfortable finger abduction and so made a brisk extension, rather than abduction, of their index finger on presentation of the cue.

### *Recordings*

EcoG was recorded in addition to acceleration in both patients. In patient DF the four electrode contacts of the epidural strip were configured to give three bipolar ECOG signals whereas in patient CO two epidural strips each consisting of four contacts were configured in an identical montage to give six ECOG signals. These were amplified and band-pass filtered between 0.9Hz and 250 Hz. Signals were digitized according to the methods outlined in chapter 2 and sampled at 1000Hz.

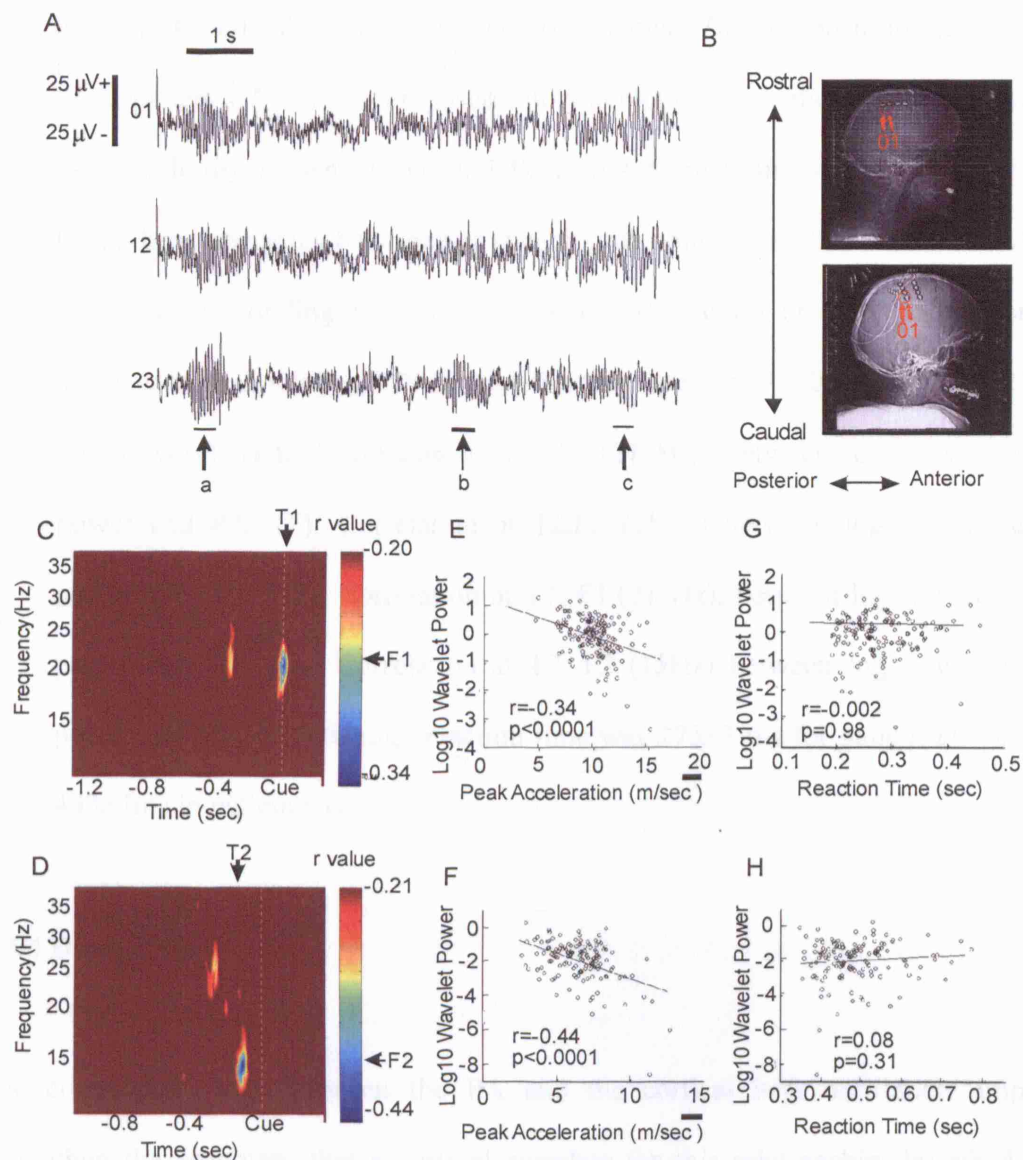
## *Analysis*

PA and RT were defined as in sections 3.1 and 3.2. To establish whether fluctuations in ECoG oscillatory activity covaried with PA or RT on a trial to trial basis the CWT of the ECoG was derived for each ms over a 1.5 second period around the cue presentation. In patient *DF* the analysis window included 0.25 seconds post cue whereas in patient *CO* this period was extended to 0.4 seconds due to a longer average reaction time. I chose a log-linear model, to describe the effect of beta activity upon response acceleration. The base 10 logarithm was used to normalize the wavelet power across trials before calculating Pearson's correlation coefficient for the wavelet power at each time point and at each wavelet scale with the PA or RT in that trial. The frequency at which the wavelet power correlated with the PA maximally was defined as the Peak Correlation Frequency (PCF). Analysis was applied to both M1 and S1 bipolar derivations.

### **3.3.3. Results**

The ECoG, like the microtremor and EMG in healthy subjects, showed phasic bursts of beta activity lasting several cycles (Figure 3.3.1, A). In the ECoG recorded from contacts 01 in patient *DF*, bursts of beta activity occurred on average every 1.4 seconds for  $1.55 \pm 0.08$  cycles of the Peak Correlation Frequency (PCF) with a maximal duration above 2SD of 4.4 PCF cycles. ECoG power in the beta band in contacts 01 was correlated with finger acceleration across RC trials ( $n=153$ ). Significant negative correlations ( $r \geq -0.20$ ,  $p < 0.01$ ) existed between wavelet power at frequencies between 18 and 24Hz and PA across trials. This was maximal 10 ms after the cue at 21Hz, where  $r = -0.34$  and

$p < 0.0001$  (Figure 3.3.1, E). In patient *CO* significant negative correlations ( $r \geq -0.21$ ,  $p < 0.01$ ) were observed at frequencies between 13 and 18Hz in contacts 01 overlying the sensory cortex. The maximal correlation occurred 120ms prior to the cue at 15Hz, where  $r = -0.44$  and  $p < 0.0001$  (Figure 3.3.1; D,F). At the PCF in this patient, oscillatory bursts at 15Hz in contacts 01 occurred on average every 0.8 seconds for  $1.89 \pm 0.25$  cycles with a maximal duration of 5.6 cycles. Thus in both patients there was a correlation between wavelet power within the beta band from the S1-ECOG and the PA. There were no correlations between wavelet power from M1 and PA and no correlations between the wavelet power from any of the bipolar signals and RT.



**Figure 3.3.5. Relationship between ECoG over sensorimotor cortex and contralateral movement execution in two patients treated for chronic pain.** (A), Example of spontaneous beta oscillations recorded from patient *DF* which demonstrates their focal as indicated by arrow *b* or diffuse character where oscillations are present across all contacts as in *a* and *c*. (B), Postoperative skull x-rays from patients *DF* (upper) and *CO* (lower) panels respectively, with electrode position and contacts with maximal correlations

labeled. **(C, D)** ECoG from contacts 01 in patient *DF* and posterior contacts 01 in patient *CO* was decomposed into wavelet coefficients around the time of a randomly presented cue and Pearson's correlation estimated between ECoG beta frequency band power at each time point for each trial and the PA of the corresponding trial in patients *DF* (C) and *CO* (D). Correlation matrices thresholded at 99% significance level ( $r = -0.20$  and  $r=0.21$  respectively). **(E)**, Correlation at T1, F1 (21 Hz), between  $\log_{10}$  wavelet power and PA. **(F)**, Correlation at T2,F2 (15Hz) between  $\log_{10}$  wavelet power and PA. **(G)**, Correlation at T1, F1 (21 Hz), between  $\log_{10}$  wavelet power and RT. **(H)**, Correlation at T2, F2 (15Hz) between  $\log_{10}$  wavelet power and RT. The average reaction time was  $275\pm 3$  ms for patient *DF* and  $483\pm 7$ ms in patient *CO*.

### 3.3.4 Discussion

The correlations seen between the PA and the cortical beta oscillation amplitude, strengthen the argument that a cortical correlate for this relationship described in the previous microtremor experiments exists. An unexpected result was that the correlations seen here were between the ECoG recorded postcentrally, and not from the precentral M1-ECoG. Misplacement of the electrodes is unlikely since their position was determined through functional stimulation. Although classical intracortical stimulation studies argued for a motor role for S1 (Schaefer, 1900; Penfield and Boldrey, 1937) and post central neurons send a large projection to the spinal chord (Bentivoglio and Rustoni,



1986; Coulter and Jones, 1977) recent investigations have revealed a sharp contrast between the functional properties of the corticospinal projections from M1 and S1. Widener and Cheney, (1997) argued that the inhibitory properties of these projections may support a role in the modulation of afferent input to the spinal chord, as originally proposed by Fetz (1968). The spatial specificity of this correlation may be the consequence of a detriment to *efferent* function of S1 rather than M1. This would be more consistent with the early time course of the correlations affecting S1 activity which is thought to precede M1 neural firing (Evarts, 1974) although admittedly, even this increase is too late to be directly affected by the oscillation at the time of the peak correlation.

Is the S1 location of the correlations seen here incompatible with the proposed corticospinal source of those seen in the microtremor? The M1 and S1 ECOG show a high degree of coherence (see chapter 5) therefore if S1 is the site of this effect the microtremor could, in theory, index S1 oscillatory activity, albeit indirectly relayed via M1. An alternative hypothesis is that the cortical and peripheral correlations reflect the effect of beta oscillations undermining the same process by oscillations generated in the spinal cord (Norton et. al. 2004). In this explanation S1 correlates with movement PA because spinal oscillations are being represented in S1 after ascending in the afferent pathways. In this explanation the lack of M1 correlations are the consequence of a separate spinal generator which bears no relation to the M1 oscillatory activity.

## **Chapter 4 : Beta oscillations are associated with altered cortical responses to afferent input.**

Why do beta oscillations prior to movement initiation prevent the optimal production of a ballistic force? The previous chapter has placed this question at the centre of this thesis. Ultimately the answer must be the consequence of disorganized motor unit recruitment since it is the orderly recruitment of motor units that provides the basis for producing effective ballistic acceleration of a limb. This in turn must involve a sub-optimal corticospinal interaction. There are many possible explanations which could explain how this situation might arise. Here I explore whether the beta oscillation heralds a change in the motor set, which preferentially organizes postural motor output, and examine the properties of the afferent and efferent pathways associated with this state.

### **4.1 Beta oscillations are associated with up-regulation of the long-latency stretch reflex.**

#### **4.1.1 Introduction**

The aims of this study are two fold. Firstly I wish to provide additional evidence to support a cortical origin to the effects of the microtremor bursts on movement acceleration seen in chapter 3. Since the evidence for a cortical origin to the transcortical reflex is now well established, an interaction between the gain of this response and the

beta oscillatory activity in muscle would be further evidence to argue for a cortical origin to the microtremor. The second question of this study is whether an exaggerated postural set could explain the suboptimal ballistic movement performance described in the previous chapter.

Since the exaggerated muscle stiffness associated with the rigidity in Parkinson's disease is correlated with long-latency stretch reflex amplitude (Rothwell et. al., 1983; Berradelli et. al., 1983), a third point tested here is whether this association is compatible with an involvement of oscillatory activity in mediating this relationship.

#### **4.1.2. Methods**

##### *Subjects*

10 right-handed healthy subjects (mean age 32 yrs, range 22 - 44 yrs, all males) were studied in these experiments.

##### *Recordings*

Microtremor was recorded with an accelerometer attached to the medial aspect of extended index finger. EMG was recorded from the FDI muscle. All signals were amplified and filtered using the settings described in chapter 2 and sampled with a

1401plus (Cambridge electronic design, Cambridge, UK) at 1000Hz before storage on a PC running Spike V6.1.

### *Paradigm*

In these experiments I used the analogue triggering method (chapter 2) to deliver stretches during microtremor beta bursts and compared these responses to those delivered at random intervals. Triggered (TS) or Random (RS) Stretches were delivered by a servo-controlled torque motor and consisted of sudden 1N-increases in tangential force delivered over 200ms. Subjects were asked to resist the adducting pull of the motor on the distal phalanx of the right index finger, so as to keep the finger in the same position. An elastic band linked the index finger to the lever of the torque motor, so that the microtremor of the finger was not dampened by inertial load (McAuley et al., 1997). Two experimental sessions were recorded on different days, in the first the only delay between triggering and stretch presentation was the 50 ms output delay imposed by the on-line electronic beta filter. In the second session there was an additional delay of 200 ms, making a total delay of 250 ms. For each session, TS and RS appeared in random order and approximately balanced number at intervals of 5-30 seconds over a period of about 15 minutes. This was repeated twice, separated by a rest period of 2-3 minutes.

### *Analysis*

Any trials with a triggering microtremor  $> 3SD$  above the mean background beta band microtremor power were rejected to limit the effect of small shifts in the position of the

finger. An average of  $70 \pm 5$  triggered stretches (TS) and  $41 \pm 2$  random stretches (RS) were analyzed in each subject for each delay (ie. zero and 200 ms) between trigger and stretch after a median of 10% of trials were rejected. The sizes of the short latency spinal stretch reflex response (M1), long latency transcortical stretch reflex response (M2) and following late (M3) response components were defined as the mean amplitude of the total rectified EMG signals measured between 32 ms and 50 ms (M1), between 54 ms and 100 ms (M2) and between 100 and 300 ms (M3) after stretch onset (Marsden et al., 1983; Day et al., 1991; Macefield et al., 1996). Since the size of the long-latency response may vary with the level of background muscle contraction (Marsden et al., 1983), the mean area of the EMG activity measured for the 400 ms prior stretch onset was subtracted from the values obtained for M1, M2 and M3. The ratios between M2 responses measured after TS and RS were also calculated. An M2 TS/RS ratio  $> 1$  indicated a greater M2 response after TS compared to RS.

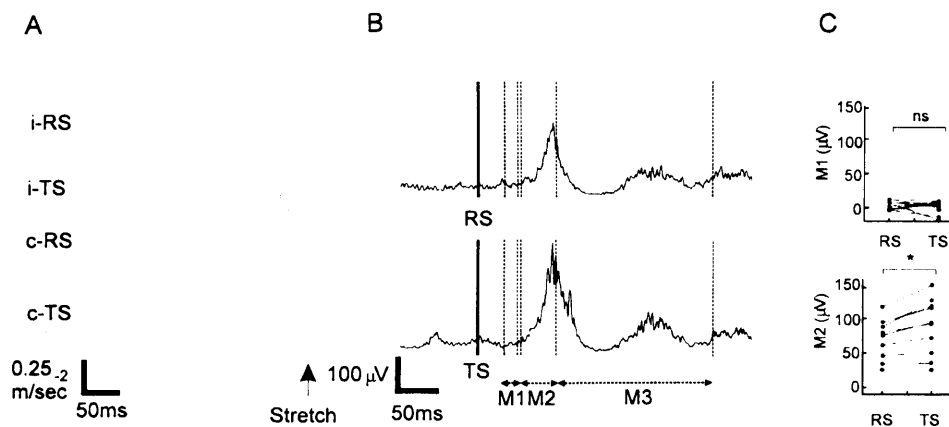
#### **4.1.3 Results**

Triggered Stretches (TS), but not Random Stretches (RS), followed the onset of bursts of microtremor in the beta frequency band and, as expected, bursts of triggering beta microtremor were unilateral (Figure 4.1.1, A). With only the 50 ms output delay imposed by the on-line electronic beta filter there was no difference between TS and RS in the short latency spinal 'M1' component (TS  $0.5 \pm 3 \mu\text{V}$ , RS  $4 \pm 2 \mu\text{V}$ ; two-tailed paired t-test,  $t(9) = -1.04$ ,  $p=0.326$ ) or the late 'M3' component of the response to stretch (TS  $34 \pm 8 \mu\text{V}$ , RS  $26 \pm 6 \mu\text{V}$ ;  $t(9) = 1.58$ ,  $p=0.148$ ). In contrast, the transcortical 'M2' component

was significantly higher after TS ( $78 \pm 13 \mu\text{V}$ ) than RS ( $62 \pm 10 \mu\text{V}$ ;  $t(9) = 4.03$ ,  $p = 0.003$ :

Figure 4.1.1 (B and C).

The exaggeration of the M2 response to stretches delivered after the onset of bursts of beta microtremor was, however, time-limited. The M2 TS/RS ratio was reduced from  $1.22 \pm 0.05$  with the 50ms delay to  $1.09 \pm 0.07$  ( $t(9) = 3.459$ ,  $p = 0.007$ ) with a total delay of 250 ms.



**Figure 4.1.1. The long-latency stretch reflex is upregulated by beta oscillations.** A, Average across all subjects of rectified beta pass band filtered acceleration recorded with the ipsilateral (i.) or contralateral (c.) accelerometer during the 500ms prior to RS or TS. Note clear transient ipsilateral increase in the beta band microtremor prior to the TS. B, Averaged EMG responses from a single participant elicited by RS ( $n = 50$  trials, upper panel) and TS ( $n = 34$  trials, lower panel). Stretch onset is given by the thick vertical line. Stretch responses were divided into 3 components: M1 (32-

50ms), M2 (54-100ms) and M3 (100-300ms). Note that the transcortical M2 response was increased after TS as compared to RS, whereas spinal M1 and late M3 responses remained unchanged. C, M1 and M2 responses (mean EMG minus background activity) for both TS and RS in 10 healthy participants. ns=not significant ( $p=0.326$ ), \* denotes  $p=0.003$ ; two-tailed paired  $t$ -tests.

#### **4.1.4. Discussion**

Firstly, these results suggest that beta microtremor bursts are associated with a modulation in the gain of a cortical reflex. This provides further support to the assumption that this peripheral manifestation of motor unit synchronization is the consequence, at least in part, of rhythmic drive from supraspinal centers. Besides from furthering this argument, do these results suggest that an explicit functional relationship may exist between these two physiological processes?

The difficulty with arguing that the beta oscillation is specifically involved in the regulation of the long-loop reflex is that the function of this reflex is far from fully understood. Nevertheless is there any convergence between the functions postulated for these two physiological processes? One interesting area is the idea of a servo-information theory. Recently, Baker et. al.(2006) have suggested that the beta oscillation may act as a test single to “probe” the peripheral motor apparatus. This idea was also proposed for the monosynaptic stretch reflex by Allum et. al (1975) who found this to be

a more fitting function since its gain was so inappropriately low for the effective correction of a perturbation. No specific mention of the long latency reflex was made by this author however the same basic concept could be applied. In both the theories of Baker and Allum, a test signal is generated and then compared with what the brain receives in the form of re-afference. It is intriguing to note therefore that in some subject's responses, (although not a feature of the example in figure 4.1.1) and those observed by others (eg. Day et. al. 1991), that the M2 response is strikingly similar in its waveform and period (50ms) to a single spontaneous beta burst seen in muscle.

A further common feature of the result presented here and those presented in the previous chapter is that the effect of beta oscillations on the reflex response continues for several hundred milliseconds after the triggering oscillation. This therefore argues that some long term state change is occurring in association with these oscillations. Again the precise mechanisms for these ongoing effects is uncertain. I will enter into more discussion on this point in the final chapter.

An unfortunate feature of the stretch response in the FDI muscle is the relative lack of M1 response. Since a particular difficulty of interpreting the previous chapter's experiments was the potential for a spinal contribution to the slowed movements, the choice of a muscle with a more robust M1 response component may have provided an important control towards establishing the source of the affect on movement speed. Future studies could look at alternative muscles or, as suggested in the pervious chapter, the affect of oscillatory activity on the H-reflex might shed light upon this critical point.



Is the enhanced long-latency response suggestive of a motor set alteration? Recently, Kurtzer et. al (2005) have argued for preferential tuning of M1 neurons to either movement or postural motor output. Furthermore, these authors speculated that oscillatory activity may distinguish these two populations of neurons. The interpretation that the long latency response upregulation may reflect the selection of a specific pool of postural neurons relies upon the assumption that this reflex is specialised to reinforce posture. Evidence for such a function is indirect; the pathological upregulation of this reflex in PD is associated with increased muscle stiffness, however, transcortical reflexes can be elicited during movements. Therefore the long-latency responses may not be explicitly associated with a specific motor set. On balance, despite the elegance of such an association beta oscillations cannot be attributed to such a specific function on the basis of these results.

## **4.2 Beta oscillations are associated with upregulation of the cortical responses to median nerve stimulation.**

### **4.2.1 Introduction**

By what mechanism could the long latency response to stretch be modified by beta oscillatory activity? There are several points along this reflex pathway which could be modified by oscillatory activity, namely the spinal cord, and the primary somatosensory and motor cortices, all of which are capable of receiving (Conway, 1995, Baker et. al.,

1997) or potentially generating (Fetz et. al, 1996) oscillations at this frequency. In this section I will test, by recording the cortical evoked responses to peripheral nerve stimulation over the somatosensory cortex, whether the beta oscillation heralds a state of altered afferent processing in the human cortex.

#### **4.2.2 Methods**

##### *Subjects*

Thirteen right-handed healthy subjects (mean age 32 yrs, range 28 - 45 yrs, 7 males, 6 females) took part in the experiment.

##### *Paradigm*

Here I tested whether the size of cortical SEPs would change when elicited during periods of elevated cortical synchrony in the beta frequency band as opposed to during random intervals. To this end, I did not use the analogue triggering mechanism used previously to trigger from microtremor bursts, but instead electrical stimuli were triggered off bursts of beta frequency band oscillations in scalp recordings of electroencephalographic (EEG) activity. This approach, however, relied on excluding the linear superimposition of EEG beta oscillations with the SEPs. Accordingly, the average duration of beta EEG bursts used for triggering was measured and bursts were found to be over by the onset of the N20 of the SEP (see later). In addition, we only averaged high-pass filtered EEG so as to attenuate components in the beta band, and tested the

success of this approach by contrasting the size of SEPs triggered off negative and positive phases of EEG beta-oscillations. Here, an absence of an effect of polarity would suggest that any change in size of SEPs following beta-triggering was not related to simple superimposition of time-locked spontaneous oscillations with SEPs.

Subjects were seated with their right forearm supported on an armrest. Subjects were instructed to maintain as constant as possible the level of contraction of the thenar muscles during the experimental run with the help of visual feedback of EMG signals presented on a computer screen. Meanwhile, a median nerve shock (0.1 ms duration) was delivered to the right wrist through bipolar electrodes (SLE Diagnostics, Surrey, UK) using a constant current stimulator (DS3 Stimulator; Digitimer, Welwyn Garden City, UK). The electrical stimulus intensity was set above sensory threshold but just below motor threshold so as to avoid thumb twitches and therefore additional delayed afferent activity.

The stimuli consisted of triggered stimuli (TS) elicited at minimal intervals of at least 5 s by the occurrence of a transient increase in beta -EEG activity in the beta- frequency band. Each TS was followed 2-3 s later by a pseudo-random stimulus (RS) (D4030 pulse generator, (Digitimer, Welwyn Garden City, UK). This procedure was used to produce the same number of interleaved TS and RS in a time-limited period and to avoid time-related influences such as fatigue that might have compromised a block design. Triggering was from bipolar EEG recorded from F3-C3 which overlies motor cortex. In the so-called “positive phase” session, the TS were presented when the on-line filtered

signal surpassed a voltage threshold defined during a 30–60 s calibration period before the recording of each run and equivalent to two to three times the root-mean square amplitude of the bandpass filtered signal. This corresponded to the positive phase of the triggering oscillation. In the so-called opposite “negative phase” session, the TS were generated when the negative phase of the oscillation was detected, that is when the filtered signal went below the inverted voltage threshold defined during the calibration period (Figure 4.2.1 B).

Runs of each polarity were repeated twice, separated by a rest period of 4-5 minutes. The 4 runs were randomly ordered. In a given session, approximately 100 TS and random RS were presented over a period of about 12 minutes. Two additional positive and negative triggered “no-stimulus” runs were also performed in which the stimulator was turned off. The latter runs enabled us to assess the quality of the triggering and the timing of beta EEG bursts independently of the presence of the SEPs (Figure 4.2.1, A and B).

### *Recordings*

Thenar EMG activity was recorded with a 9mm silver-silver chloride electrode over the belly of the abductor pollicis brevis and one over the proximal phalanx of the thumb. In addition to the triggering EEG recorded from F3-C3 I also recorded EEG from C3-P3, overlying sensory cortex. All signals were amplified and filtered according to the settings outlined in chapter 2, prior to A-D conversion via a CED 1401 analogue to digital

converter (Cambridge Electronic Design, Cambridge, UK) and sampling at 6 kHz using Spike 5.5 software (Cambridge Electronic Design, Cambridge, UK) running on a PC.

### *Analysis*

After artefact removal (EEG parts contaminated by EMG), the measurement of the SEP was implemented off-line. C3-P3 EEG was first down-sampled 1 point in 5 to 1200 Hz and high-passed filtered (FIR, cut frequency: 36.3 Hz, transition gap: 7.7 Hz). This procedure was used to make sure that beta- frequency band oscillations would not superimpose on SEPs measured after TS. Trials were averaged separately with respect to RS and TS in each subject for both positive and negative sessions. The N20 and P30 were defined respectively as the peak negativity between 16 and 24 ms and the peak positivity appearing after the N20 and before 35 ms. In classical monopolar recordings of SEPs the maximal amplitude of the cortical N30 has previously been shown to be over the central region (Valeriani et al., 2000); thus with an active electrode over the parietal region and a reference electrode over the central region a corresponding P30 is recorded, although I cannot rule out an additional contribution from the P22/25 component reported in monopolar SEPs. SEP peak amplitudes were measured from the zero baseline and latencies defined as the interval between the stimulus onset and the peak of each potential of interest. The data from two subjects were excluded because their N20 amplitude after RS was inferior to three standard deviations above the mean background EEG (measured from 100 ms to 50 ms before the stimulus onset). Further data analyses were performed on the 11 remaining subjects.

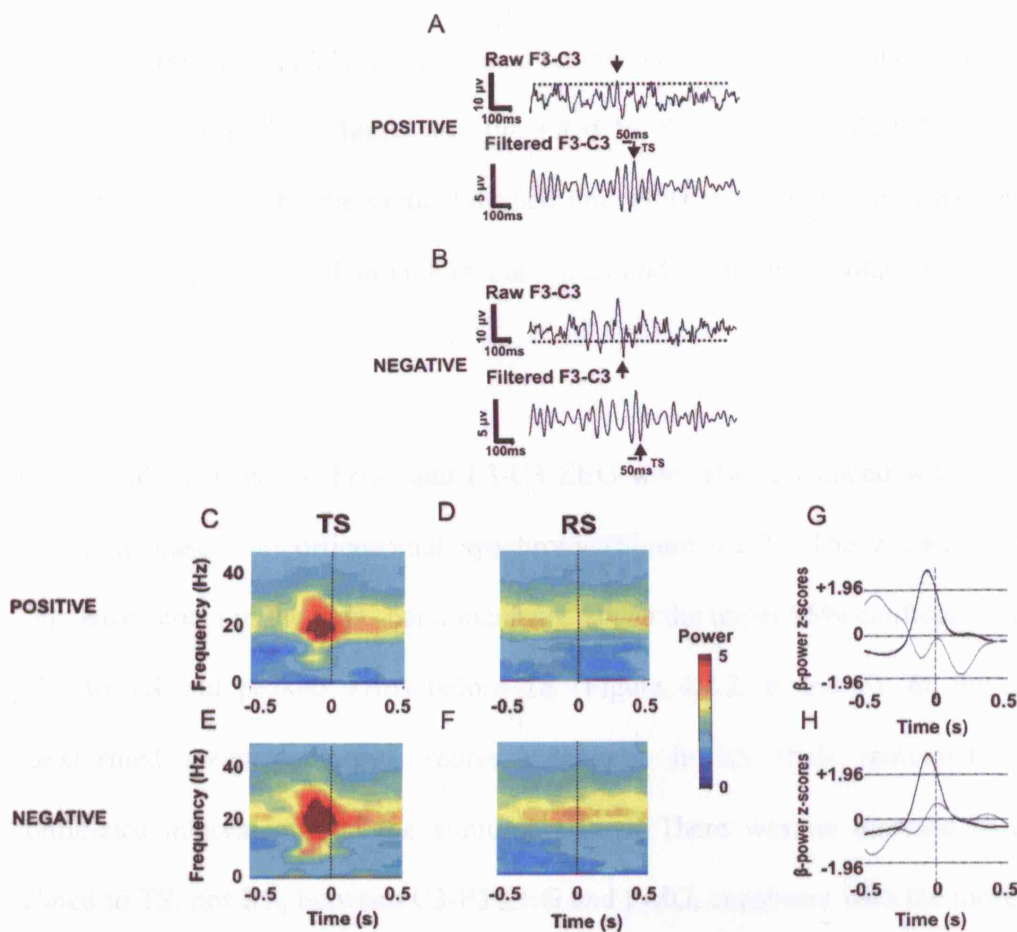
To verify that increases of beta-band activity in the fronto-central EEG were associated with an elevated descending drive, thereby at least partially involving motor cortex, we evaluated cortico-muscular coherence in “no stimulus” trials. In addition, to verify the quality of our triggering off beta-band activity, I evaluated EEG power in “no stimulus” trials. All signals were analyzed at 1200 Hz. Estimates were derived of event-related F3-C3 EEG power and coherence between F3-C3 EEG and thenar EMG, and between C3-P3 EEG and thenar EMG with respect to TS and RS. FFT based spectral analysis was performed using overlapping blocks of 512 data points, shifted by 1ms. The matrices of event related power for each frequency within the beta-band (13 -35 Hz, frequency resolution: 2.3 Hz) for each subject and triggering polarity during triggered and random trials were calculated. These values were then averaged across subjects and across all frequencies in the beta band (13 -35 Hz), separately for triggering polarities, to give two power scores at each time point for triggered and random trials. These mean power scores were z transformed over a 1.286s period starting 785ms before stimulus onset to confirm whether or not power within each condition was increased around the time of triggering.

Analysis of event related coherence for each frequency within the beta-band (13 -35 Hz, frequency resolution: 2.3 Hz) for each subject and triggering polarity during triggered and random trials was performed. A value of 10 was attributed when EEG-EMG coherence was significant ( $p > .05$ , estimating significance levels using the approach described by Halliday *et al.*, 1995) at a particular frequency or time bin and 0 when it was not. These values were then averaged across all triggering polarities (as no difference in

SEP means as a function of triggering polarity were found –see results-), subjects and all frequencies in the beta band, to give a single coherence score at each time point for triggered and random trials. These mean scores were z transformed over a 1.286s period starting 785ms before stimulus onset. This non-parametric approach was preferred, as the data could not then be dominated by high corticomuscular coherences in one or two subjects. The latter is important because corticomuscular coherence may vary considerably between subjects.

#### **4.2.3 Results**

Transient increases of activity in the beta-band (Figure 4.2.1 A and B) in C3F3 were associated with the TS trials in the all subjects. These increases were used to trigger electrical stimuli with the 50ms delay inherent in the on-line filtering device. The adequacy of this triggering was confirmed in the group average event-related power plots, which showed a phasic elevation of beta-band F3-C3 EEG prior to and during TS but not RS (Figure 4.2.1 C, D, E and F). The z transformed mean power scores in the beta-band increased above the upper 95% confidence limit 114ms prior to TS and peaked 58ms before TS with positive thresholding and 113ms prior to TS and peaked 55ms before TS with negative thresholding. In contrast there was no consistent power modulation in the RS trials, which was reflected in the z transformed mean power scores remaining within the confidence interval around the stimulus period (Figure 4.2.1 G and H).

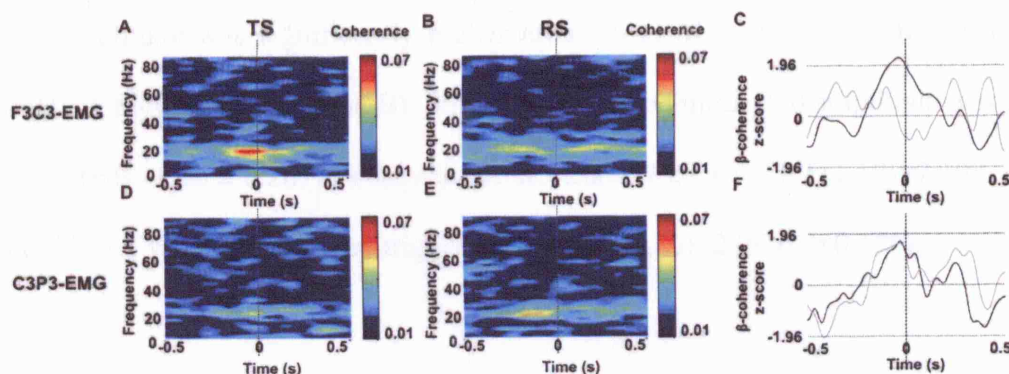


**Figure 4.2.1. Analogue triggering from EEG beta oscillations.** (A and B) Raw F3-C3 EEG of one subject before and after beta-band filtering using the on-line electronic device that imparted a 50 ms delay. As threshold (thin horizontal line) crossing was detected, either at the positive or negative phase, off the beta -band filtered signal, there was also a 50 ms delay before stimuli were triggered. Mean event-related F3C3 EEG power averaged across 11 subjects and around TS (C and E) and RS (D and F) when triggered off positive or negative polarity (stimulator off). Power is in arbitrary units. (G) Z transformed averages of the beta -frequency band power scores for both



positive and negative triggering polarities with respect to TS (black line) and RS (grey line). Analyses performed on the “no-stimulus” signals. Ninety-five percent confidence limits are illustrated by the horizontal dotted lines and stimulus onset by the vertical dashed line. Note the increase of power in the beta-frequency band around TS but not around RS for both polarities.

The periods of elevated beta-band F3-C3 EEG were also associated with simultaneous phasic increases of corticospinal synchrony (Figure 4.2.2). The z transformed mean coherence scores in the beta -band increased above the upper 95% confidence limit 86ms prior to TS and peaked 37ms before TS (Figure 4.2.2, E and F). In contrast, the z transformed mean coherence scores calculated in RS trials remained within the confidence interval around the stimulus period. There was no increase in coherence related to TS, nor RS, between C3-P3 EEG and EMG, consistent with the more posterior localization of the parieto-central EEG electrode pair.



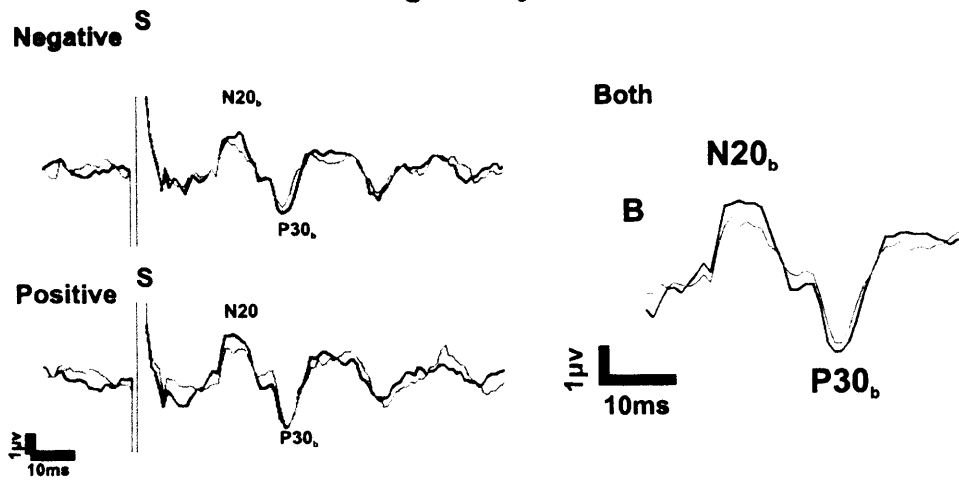
**Figure 4.2.2. Mean cortico-muscular and F3-C3 - C3-P3 synchrony in 11 subjects** Mean cortico-muscular synchrony in 11 subjects: (a) Mean coherence between F3-C3 EEG and EMG (top panel), and between C3-P3 EEG and EMG (lower panel) averaged around TS (left panel) and RS (right panel), respectively. (b) Z transformed averages of the beta-frequency band coherence scores (averaged across both triggering polarities). F3-C3 EEG-EMG (top panel) or C3-P3 EEG-EMG (middle panel) coherence with respect to TS (black line) and RS (grey line). Note that F3-C3 EEG-EMG coherence was significant at the time of TS but not RS. C3-P3 EEG-EMG coherence did not exhibit such a change. Analyses performed on the “no-stimulus” signals. Ninety-five percent confidence limits are illustrated by the horizontal dotted lines and stimulus onset by the vertical dashed line.

Repeated measures ANOVA of the N20 and P30 amplitudes with factors “type of trial” (TS vs RS) and “triggering phase polarity” (negative vs positive) were performed. Analyses showed a main effect of trial type (TS vs RS) on the N20 amplitude

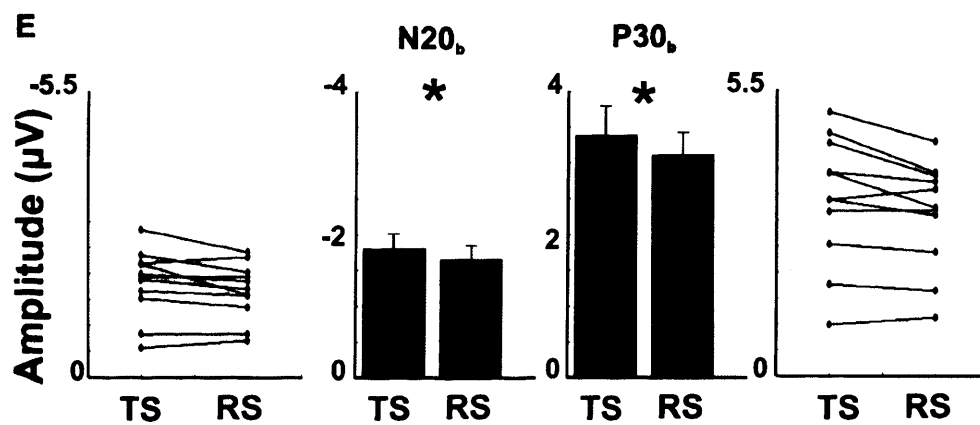
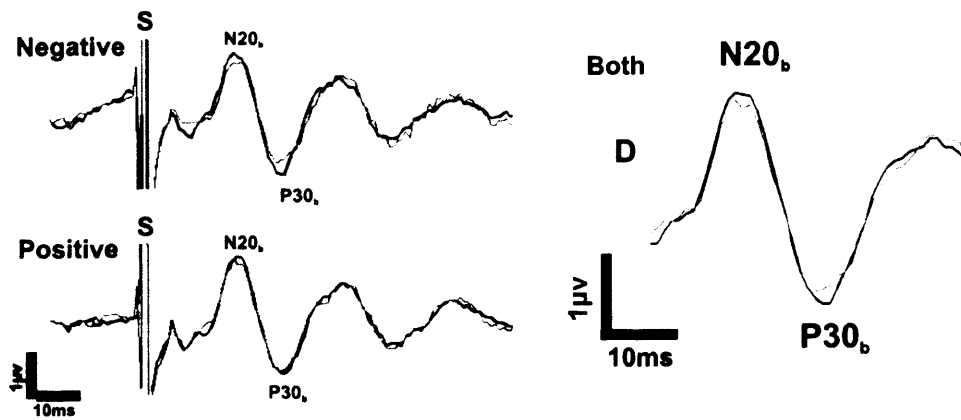
( $F(1,10)=5.618$ ,  $P=0.039$ ) but no effect of the oscillation phase ( $F(1,10)=0.109$ ,  $P=0.748$ ). N20 amplitude was significantly higher after TS ( $1.81 \pm 0.19$ ) than RS ( $1.66 \pm 0.16$ ,  $P=0.039$ , Figures 4.2.3, A and B). Similarly, enhanced mean P30 amplitude was also seen in TS trials ( $1.42 \pm 0.26$ ) as compared to RS trials ( $1.29 \pm 0.23$ ,  $F(1,10)=7.197$ ,  $P=0.023$ ) and this too was unaffected by triggering phase ( $F(1,10)=2.096$ ,  $P=0.178$ ).

**Figure 4.2.3 High-pass filtered EEG responses to median nerve stimulation.** Averages across all subjects (C) and of one typical subject of C3-P3 EEG (A) recorded when stimuli were triggered (black line) off the positive or negative phase of the beta-frequency oscillation or triggered randomly (grey line). Averages across triggering polarities are also presented in the insets B and D. Stimulus onset is given by the stimulus artefact (S). Note the emergence of N20 and P30 potentials. (E) Mean amplitude and standard errors of the means represented by error bars of N20 and P30 for both TS and RS in 11 healthy subjects. \* denotes  $p<.05$ . Both N20 and P30 potentials were higher after TS than after RS (N20 7/11 increased; P30 8/11 increase) but were not affected by the triggering phase. Thus, data presented here are from the average responses obtained for both the negative and positive phase triggering algorithms.

# **A** **Single subject**



# **C** **All subjects (n=11)**



#### **4.2.4. Discussion.**

These results suggest that cortical beta oscillations coherent with the spinal motor output may be associated with heightened cortical sensitivity to somatosensory input. Since the SEP components studied here are thought to be generated by dipole sources in the post-central gyrus (Allison, 1991), the implication of these results is that an oscillation that engages M1's cortical output can influence the response properties of neurons in S1 (specifically areas 2 and 3b). Before considering the potential neural mechanisms that may be accountable for this result I will discuss some of the caveats required in the interpretation of this data.

In this study, both triggering phases produced a symmetrical increase in the response amplitude, ruling out the possibility of a simple superimposition of the evoked and triggered ongoing EEG. Although the power of the beta oscillation at the time of the N20/P30 responses was not above the chance level, the possibility that the triggering produced an artificial phase stationarity that persisted until this time cannot be discounted. This could, in theory have produced a more stable background of ongoing activity across trials which in turn improved the SNR of the cortical response and hence provided greater average amplitude. Even if analysis of the phase revealed that such a stationarity were occurring, then the only way of eliminating such an interaction, would be to demonstrate an interaction between the oscillation and the SEP on a single trial basis. This is clearly not feasible in the context of scalp recordings.

Therefore, with some caution in mind, it is interesting to ask what neural process might contribute to the facilitation seen here. At a central level, an intuitive explanation would be that the oscillation, which represents synchronized post synaptic membrane potential fluctuation's may promote correlated discharge of the neuronal population that engages in the response (Salinas and Sejnowski, 2001). This interpretation relies upon two assumptions however. Firstly the membrane potential oscillations should be related between the motor cortical population used to trigger the stimuli and the population of neurons in the sensory cortex that generate the response. This can be justified since coherence between M1 and S1 has been observed in the monkey (Brovelli, 2004; Murphy and Fetz, 1996) and in the human (last chapter of this thesis). One problem is that at the time of the N20 or the P30, the beta power between the TS and RS trials are statistically the same. Therefore if we are to assume that power of the oscillation (amplitude) is proportional to the number of neurons receiving synchronised input, then this cannot account for the difference between the two states. The only difference between the triggered and the randomly evoked responses is in the degree of oscillatory synchrony in the corticospinal tract prior responses. Therefore, the only feasible explanation of an intracortical effect could be a short term-plastic change that is pervasive across a coherent motor and sensory cortex.

If a short term plastic effect could not account for this result then the interaction between the triggered oscillatory activity and the evoked volley must have occurred prior to the response arriving at the cortex. Could a reduction in subcortical gating of the afferent volley have resulted in the greater cortical responses? Corticospinal projections are thought to be very effective at presynaptically inhibiting cutaneous afferents (via inhibitory interneurons acting at the dorsal root nucleus ([Seki et. al., 2004, Andersen et. al., 1962a] or the cuneate nucleus [Andersen et. al., 1962b]), which are thought to make a major contribution to the median nerve SEP (Allison et. al., 1991). Although I provided evidence for the spinal involvement of the triggering oscillations through corticomuscular coherence it remains to be seen why these triggering oscillations should disrupt the effectiveness of this projection in mediating afferent inhibition. Considering the feasible possibility that the spinal cord is the generator microtremor oscillations, it would be interesting to repeat these experiments with this signal as the trigger for the stimuli. The potential concordance with a conceptual association between beta oscillations and slowed movements is interesting nonetheless: the inhibition of cutaneous reflexes is reduced in parkinsons's disease (Fuhr et. al., 1992) and the recruitment threshold of motor units is also thought to be increased by cutaneous afference at the spinal level (Stephens et. al., 1978).

Irrespective of the precise mechanism at work here, the implications of this study are that the oscillation may be involved in organizing the cortical sensory representation afferent input in a manner that is relevant to the motor set at the

time. This role in sensorimotor integration may be exemplified in the up-regulation of the long latency response to stretch seen in the previous chapter.

### **4.3 Combined studies of TMS and online wavelet fitting to the EEG.**

#### **4.3.1 Introduction**

A recurring limitation of the online analogue filtering technique used in the experiments described previously, was that the intrinsic delay of the filter consistently prevented a direct interaction between the stimulus and the oscillatory activity in real time. The conclusions of these experiments were consequently limited to speculations of a plastic processes and so forth. I therefore wished to develop a method to definitively test the properties of beta oscillations as they were occurring rather than after they had occurred.

The second aim of this study was to test the practical feasibility of combined TMS and EEG studies with online triggering with the idea to examine the excitability of the motor cortex during oscillatory activity. The principle hypothesis here was that if the oscillation reflects input into pyramidal output neurons, then fluctuations in excitability should be related to the oscillatory state of the cortex. The second test was more specifically aimed at whether the intrinsic generating mechanism of these oscillations involved an alteration in the inhibitory networks related to pyramidal neurons. This was tested by probing intracortical networks with short latency cortical inhibition (Kujirai, 1991). Since this is thought to be mediated by



GABAergic networks, this was deemed to be a relevant question in the context of beta oscillatory generation, where these networks have also been implicated (Glaze, 1990) in the generation of the oscillatory activity.

#### **4.3.2 Methods**

##### *Subjects*

Ten healthy subjects (2 female) mean age 31 (range 24-38) years with were recruited.

##### *Recordings*

The motor cortex hand area was localised functionally by eliciting Motor evoked potentials in the FDI with TMS (Magstim 200, Rochdale, UK). The hand area “hotspot” was defined as the site of stimulation at which TMS evoked the most consistent motor evoked potential (MEP) at the lowest stimulus intensity in the FDI muscle. Two Silver-Chloride electrodes were attached to the scalp either side of the FDI area in the anterior-posterior plane with a total interelectrode distance of 2 cm. EMG was also recorded from Abductor Digiti-Minimi (ADM). Bipolar EMG and EEG were amplified and filtered at the settings described in chapter 2. All signals were sampled for A-D conversion at 5000Hz using a 1401 (CED, Cambridge) and recorded by a PC running Signal v3 (CED, Cambridge, UK).

##### *TMS and online triggering.*

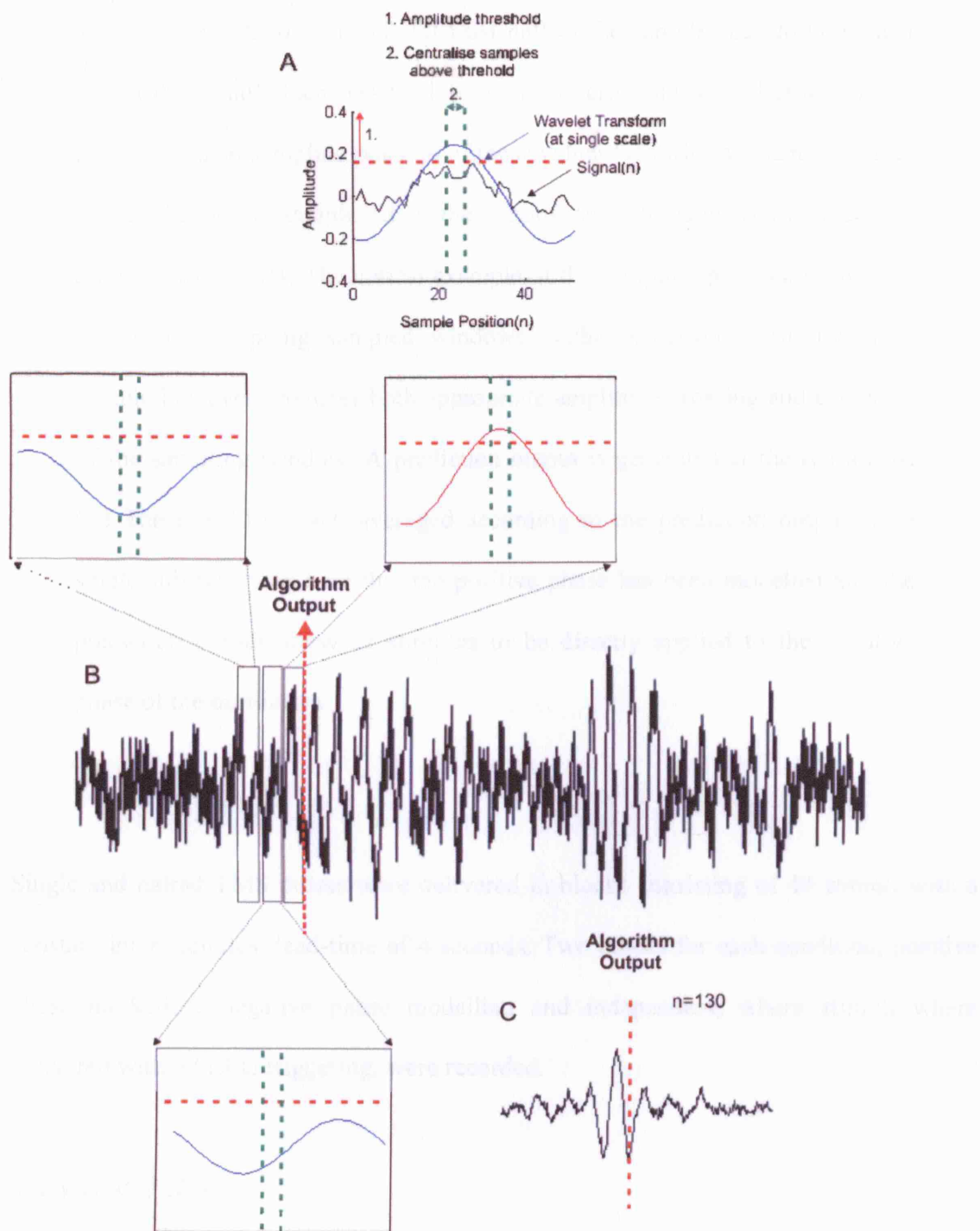
The effects of beta oscillations on single and paired pulse TMS were tested. A stimulator intensity that evoked a Motor evoked potential of approximately 1mV was used as the test response. In the paired pulse trials this was preceded by a 3ms conditioning pulse at 80% of the active motor threshold (AMT). In 3 subjects the conditioning stimulator output had to be further adjusted from this level to produce a baseline level of approximately 50% inhibition in the FDI muscle. Single and paired pulse stimuli were delivered pseudo-randomly within each of the experimental blocks.

I devised an online wavelet based algorithm for detecting oscillatory activity and delivering the TMS pulses on either the positive or negative phases of the oscillation. The basic assumption of this technique was that beta oscillations occur in phasic bursts often lasting several cycles. By fitting a wavelet of the same frequency as the EEG beta to one cycle we could assume that the stimulus would occur with good probability during a phasic burst. Bipolar EEG was sampled at 1000Hz using a second 1401 interfaced with MATLAB v7.1 using MATCED32 (written by Jim Colebatch). Non-overlapping windows the width of which corresponded to the period of the modelled waveform (eg. 20Hz , 50ms period, 50 samples) were sampled for wavelet analysis. To minimise computational delay I used the convolved wavelet transform of Torrance and Compo at a single wavelet scale (pseudo-frequency). (See Chapter 2).

Two criteria were used to define a satisfactory “fit”. Firstly at least half of the real values of the wavelet transformed samples in the sampled window had to be above (positive phase

modelling) or below (negative phase modelling) an empirically derived threshold. This criterion ensured that the sampled waveform was of a suitable “likeness” to the frequency of the wavelet selected offline. The sign of this threshold had to be appropriate for the phase being modelled. To ensure stationarity of phase between windows which contained a suitably robust oscillation the median sampling position of those samples greater or less than the required threshold had to be equal to half the window size  $\pm 3$  samples. This second criterion biased predictions to only occur when the peak or trough (depending upon the phase being modelled) occurred in the centre of the sampling window. The allowance of 3 samples in jitter was found to be a suitable compromise between phase stationarity and the frequency of the algorithm’s output. A schematic illustration of this algorithm is illustrated in figure 4.3.1.

The threshold was empirically derived during a training set in which the EEG was averaged according to the algorithm’s output times. This training set with TMS artefact free trials was used to assess the quality of the algorithm’s performance offline.



**Figure 4.3.1 Wavelet based online fitting algorithm.** (A) Criteria for defining a suitable fit. The wavelet transform of the EEG sampled in 50ms windows had to have a specified number of samples above a predefined

amplitude threshold. Typically at least half of the samples had to be greater than a threshold which was tending towards zero. The second criterion was that the median sampling position of these values was within 3 samples either side of the central sample. (ie. If the window was 50 ms in width the central sample was 25). (B) Theoretical example of the sampling process. In the first two non-overlapping sampled windows neither criterion is fit, the third sample however produces both appropriate amplitude crossing and centering of the sampling window. A prediction output is generated at the red arrow. (C) The raw EEG back averaged according to the prediction outputs in a single subject. Note here that the positive phase has been modelled and the prediction output allows a stimulus to be directly applied to the negative phase of the oscillation.

Single and paired TMS pulses were delivered in blocks consisting of 40 stimuli with a constant inter-stimulus dead-time of 4 seconds. Two blocks for each condition, positive phase modelling, negative phase modelling and independent, where stimuli were delivered without EEG triggering, were recorded.

#### *Analysis of MEP's*

The peak to trough amplitude of the test and conditioned MEP in both FDI and ADM were measured offline in Signal. Any trial with EMG activity greater than 50 $\mu$ V within

100ms prior to the stimulus was rejected as were responses elicited by TMS less than 50 $\mu$ V. Responses greater than 3SD of the mean were assumed outliers and not included in further analysis.

### *Offline Signal analysis*

To establish the quality of the triggering produced by the algorithm we analysed the trials without artefacts produced by the TMS stimulus. Offline continuous wavelet transforms (CWT) were performed at wavelet scales with corresponding frequencies between 12 and 65Hz with an approximate resolution of between 1.4Hz and 0.3 Hz for the higher and lower frequency scales respectively. The analysis window was centred around the algorithm's output time with an offset  $\pm$  1second. Time-frequency maps were averaged across the ten subjects. Before averaging, the power at all frequencies and time points was normalized by the power (averaged across time) derived from shuffling the signal N times where N was equal to the number of trials analysed. This procedure prevented large differences in the wavelet derived power between subjects from biasing the average. One assumption of averaging time-frequency derivations of power is that the frequency of oscillatory events is consistent across and within subjects at any time. To prevent underestimation of the power caused by frequency "jitter" across and within subjects we analysed each trial individually. As before, the CWT was performed on trials without TMS. The wavelet power at the scale which optimally modelled the signal 50ms before the algorithm's output was averaged over the N trials used in the analysis. This average

was normalized by repeating the analysis on randomly shuffled epochs and selecting the same frequencies as modelled in the real data for the shuffled average.

Analysis of the phase of the beta oscillation at which the TMS pulse was delivered was performed by deriving the complex argument of the CWT at the scale which optimally modelled the EEG in a 50 ms sample prior to the TMS pulse. Circular statistics were used to calculate the mean angle and its circular variance for each subject in both paired and single pulse trials.

Results are expressed in terms of the mean  $\pm$  S.E.M, or when describing circular variables in terms of the circular mean  $\pm$  circular dispersion.

#### **4.3.3 Results:**

##### *Online Wavelet triggering*

The raw EEG averaged to the time of the algorithm's output when modelling the positive or negative phases is illustrated in figure 4.3.2. An average of  $85 \pm 9$  trials were used to analyse the performance of the waveform fitting procedure offline for each subject in both the positive and negative phase sessions. Wavelet analysis in the 12-65Hz range revealed a power increase in the positive phase modelling trials centred around the time of the algorithm's output at 22 Hz (Figure 4.3.2, B). In the negative phase modelling trials, two power maxima were seen at 26 and 15 Hz respectively (Figure 4.3.2, C). When

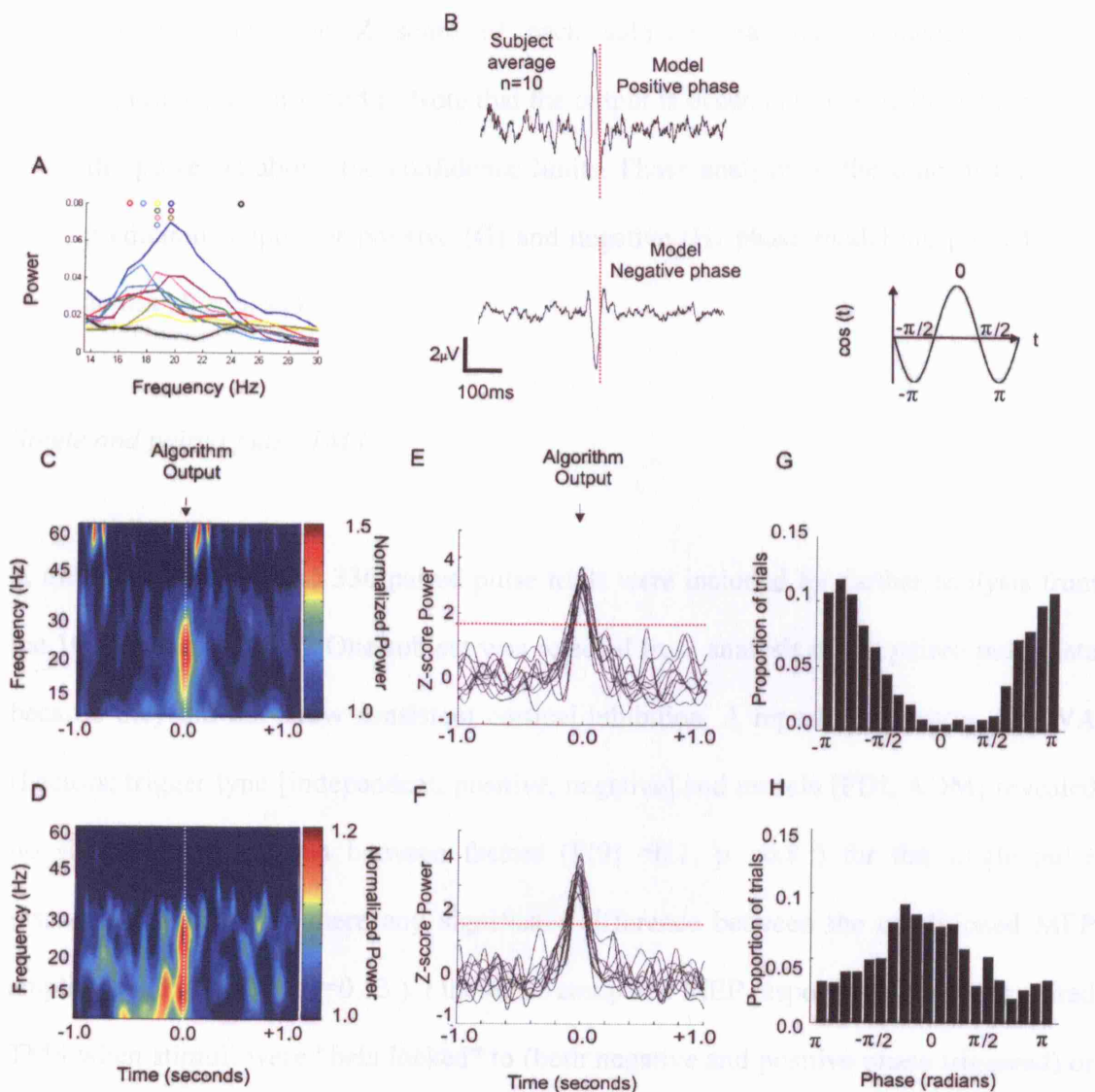
trials were analysed on a single trial basis the mean triggering frequency was 19 and 18 Hz for the positive and negative modelling sessions respectively. A more detailed breakdown of the frequency components displayed some differences between modelling the positive and negative waveforms of the EEG. In the negative phase modelling sessions the mu (<13 Hz), low-beta (13-17Hz) and high-beta (18-30Hz) frequency bands contributed to 24%, 19% and 37% of the total power in the population averaged CWT 50ms prior to algorithm output. In contrast, the positive phase modelling in the same bandwidths contributed 17%, 19% 37%. Therefore, despite the mean triggering response being around 18Hz in both sessions, there was an asymmetry at lower frequencies between these two modeling types.

Time evolved estimates of each subject's average power from the analysis of individual trials is illustrated in figure 4.3.2 ,D and E. Z-transformed power increased above the 95% confidence limit on average 143ms and 135ms prior to the algorithms output and decreased below this level 97 and 89 ms after the output in the positive and negative trials respectively. On average the power maxima occurred  $26 \pm 5$  ms prior to the algorithm's output.

Analysis of the triggering oscillation's phase at the time of the algorithm's output is illustrated in figure 4.3.2, F and G. The mean phase at this time was  $4.94 \pm 1.42$  radians in the positive phase modelling trials with the negative modelling trials producing a mean of  $1.15 \pm 5.79$  radians.



In all, analysis of the algorithm's performance using trials without the TMS artefact suggested that this technique was appropriately selecting epochs of EEG where oscillations in the beta band were most prominent. Furthermore, within oscillation phase was also being discriminated, albeit with less sensitivity when the negative was modelled compared to the positive.



**Figure 4.3.2** Offline analysis of wavelet fitting algorithm performance.

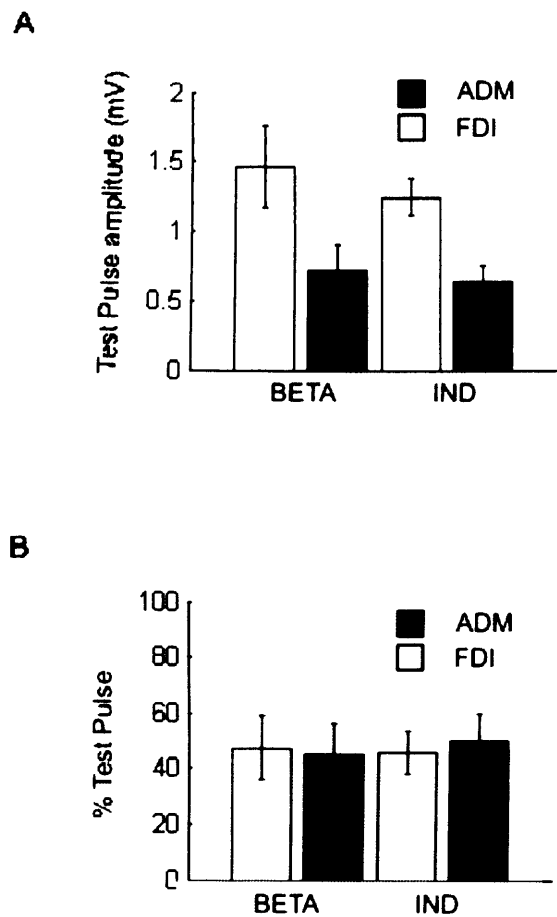
(A) Power spectrum of spontaneous EEG in the ten subjects. Each colour

represents a subject. The corresponding coloured circle illustrates the peak frequency of the spontaneous EEG spectrum. Seven out of the 10 subjects had a peak in their power spectrum that was at 19 or 20Hz. (B) Raw EEG average of 10 subjects positive and negative modelling sessions. C and D, Time frequency wavelet power averaged across the 10 subjects after normalisation. The Z score of each subjects maximal frequency are superimposed in E and F. Note that the output is occurring on a period where the power is above the confidence limits. Phase analysis at the time of the prediction output for positive (G) and negative (H) phase modelling pooled across all subjects.

### *Single and paired pulse TMS*

A total of 325 single and 336 paired pulse trials were included for further analysis from the 10 subjects recorded. One subject was rejected from analysis of the paired pulse data because they did not show consistent cortical inhibition. A repeated measures ANOVA (Factors; trigger type [independent, positive, negative] and muscle [FDI, ADM] revealed no significant interaction between factors ( $F[9] = 0.1$ ,  $p = 0.8$ ) for the single pulse responses, neither was there any significant difference between the conditioned MEP amplitudes ( $F[8] = 2.2$ ,  $p = 0.13$ ). I therefore compared MEP responses to single or paired TMS when stimuli were “beta locked” to (both negative and positive phase triggered) or “independent” of the EEG. The mean MEP responses to single or paired pulses simulation in these two conditions are illustrated in figures 4.3.3, A and B. A repeated

measures ANOVA (Factors; trigger type [independent, betalocked] and muscle, [FDI and ADM]) revealed no interaction between trigger type and muscle (ANOVA [single],  $F[9] = 0.25$ ,  $p = 0.62$ ; ANOVA [ paired] ,  $F[8] = 0.06$ ,  $p = 0.75$ ). These results suggested that the presence of a peri-stimulus oscillation had no effect on the response amplitude elicited by TMS or the degree of short latency inhibition.



**Figure 4.3.3** MEP in FDI and ADM to single and paried TMS pulses locked to the beta oscillation or delivered independently of the EEG. No effect on the responses elicited to single pulse (A) in either muscle was seen

when the TMS pulse was delivered on the beta oscillation. Likewise, no changes in the degree of conditioning by a subthreshold pulse (B) were observed.

#### **4.3.4. Discussion**

The aim of these experiments were twofold. Firstly I was interested in the methodological problem of developing an online waveform fitting algorithm which could overcome some of the short comings of the analogue method used previously. Secondly, I wished to test the hypothesis that corticospinal excitability and intracortical inhibitory networks could be altered during these oscillations. I found no evidence to suggest that this was the case. However, these results cannot be interpreted to suggest that no direct relationship exists between the oscillation and pyramidal neuron excitatory or inhibitory network activity. It seems most likely that the technique used here to examine these networks, TMS, is too insensitive to examine these networks particularly when only a single conditioning ISI is tested. Of course, the possibility that the EEG provides a poor spatial representation of individual muscle excitability, for the same reasons that EEG –microtremor correlations were very weak must also be considered. It would be interesting to use microtremor bursts to trigger TMS pulses, in light of the success of this signal in predicting the PA, in future studies. Nevertheless, I will not labour this discussion on what is a negative finding.

The positive finding of this study is that there is a clear benefit to the wavelet algorithm in that the stimulus presented here occurred during a consistently high period of beta activity. Of course in this case there is no peripheral delay, however, nearly two complete cycles of beta activity were still accessible to any arriving neural response. Therefore using this algorithm to trigger transcortical reflexes or median nerve stimuli would provide more confident interpretation of the interactions between oscillatory activity and afferent responses initiated in distal sites. The algorithm was also able to allow specific distinction within an oscillatory phase. It has been recently applied in our lab to positive effect (Androulidakis et. al, 2006 Appendix).

Future work may be needed to improve the frequency specificity of the fitting. I found that the ability to distinguish beta oscillations was dependant upon a “simple” spectral content in the EEG. Subjects with dominant 10Hz activity would frequently confound the triggering, these subjects were therefore not used in this study. This low pass biasing may have been a function of the near zero amplitude threshold used for the fitting in this study. If the oscillation were at 20Hz the criteria requiring half of the samples to be above a near zero threshold could not have been reached, the only value in which half of the samples of a 20Hz waveform are above or below (depending upon the threshold sign) is zero. This therefore explains the 19 and 18 Hz average triggering frequencies for the positive and negative sessions. Only oscillations with a period longer than the sampling window could have half of their values greater than a near zero amplitude. These properties of the algorithm on one hand make it a very effective filter of signals up to the

period to the sampling window but on the other make it susceptible to large amplitude low frequency (eg. alpha) EEG components which can masquerade as beta oscillations. Further criteria may be implemented in future versions to improve the specificity of the lower frequency cut of its band pass.

## **Chapter 5: Organisation of sensorimotor oscillations during a voluntary movement.**

### **5.1 Sensorimotor coherence and resetting of beta oscillation phase during preparation for voluntary movement.**

#### **5.1.1 Introduction**

The question that concerns the following experiment is how oscillatory activity is organized with respect to a voluntary movement within the primary motor and sensory cortices. This is of interest for two reasons. Firstly, the previous chapters have suggested that oscillations in S1 can affect motor output (chapter 3) and that oscillations in M1 can, conversely, affect the processing of sensory input (chapter 4). The cortical origin of these observations would be strengthened if beta oscillations in these two regions show some degree of covariance. Secondly, previous studies have implied that beta oscillations are principally concerned with posture or are an “idling” rhythm (Pfurtscheller et. al., 1997). This interpretation has come from the principle effect of movement on the oscillatory activity in the beta band being a desynchronisation with a corresponding power reduction prior to and during the movement. These conclusions assume however that an oscillation is only of interest to the brain if it is large in amplitude, and therefore when small, oscillations are functionless. The question therefore presented in this chapter is whether despite their small amplitude, the organization of beta oscillatory phase may be critically involved in movement *per se*.

### 5.1.2. Methods

#### *Patients*

Three patients with electrode strips implanted within the sensorimotor cortex for the treatment of chronic pain syndrome were studied. Four 4 mm electrodes separated by 1 cm were localized to the hand areas of M1 and S1 using the intraoperative procedure described in chapter 2. All patients were off medication and were recorded at least three days post-operatively. Case 1 was a 57 year old male with a 7 year history of trigeminal neuralgia and multiple sclerosis. Case 2 a 37 year old male with a 3 year history of trigeminal neuralgia. The final case was a 49 year old female with a 2 year history of upper limb pain after a stroke affecting the the right parietal cortex.

#### *Paradigm*

I used the same visually cued simple reaction time as described in chapter 3. Patients responded with a brisk finger movement when a visual cue was presented (LED). In cases 1 and 2 this movement consisted of an abduction of the index finger, in case 3 finger flexion was made. During the intervals between cues the patients were instructed to keep their index finger extended. Timing of the cues was determined manually with an approximate intertrial period of 5 seconds.



### *Recordings.*

In the recordings made of cases 1 and 2 bipolar derivations were amplified and filtered using the standard settings outlined in chapter 2, and sampled at a frequency of 1000Hz. In case 3 the EcoG was amplified 10000 times filtered between 1 and 100 Hz and sampled at 184Hz using a portable amplifier (Biopotential analyzer Diana, Sechenov Institute of Evolutionary Physiology and Biochemistry, St-Petersburg, Russia) and custom built A-D converter.

The reaction time was defined as the time between cue onset and the onset of the initial acceleration deflection recorded from an accelerometer (EGAXT-50; Entran, Fairfield, USA) attached to the outstretched index finger. Accelerometer signals were amplified and low pass filtered at 100Hz with no high pass filtering.

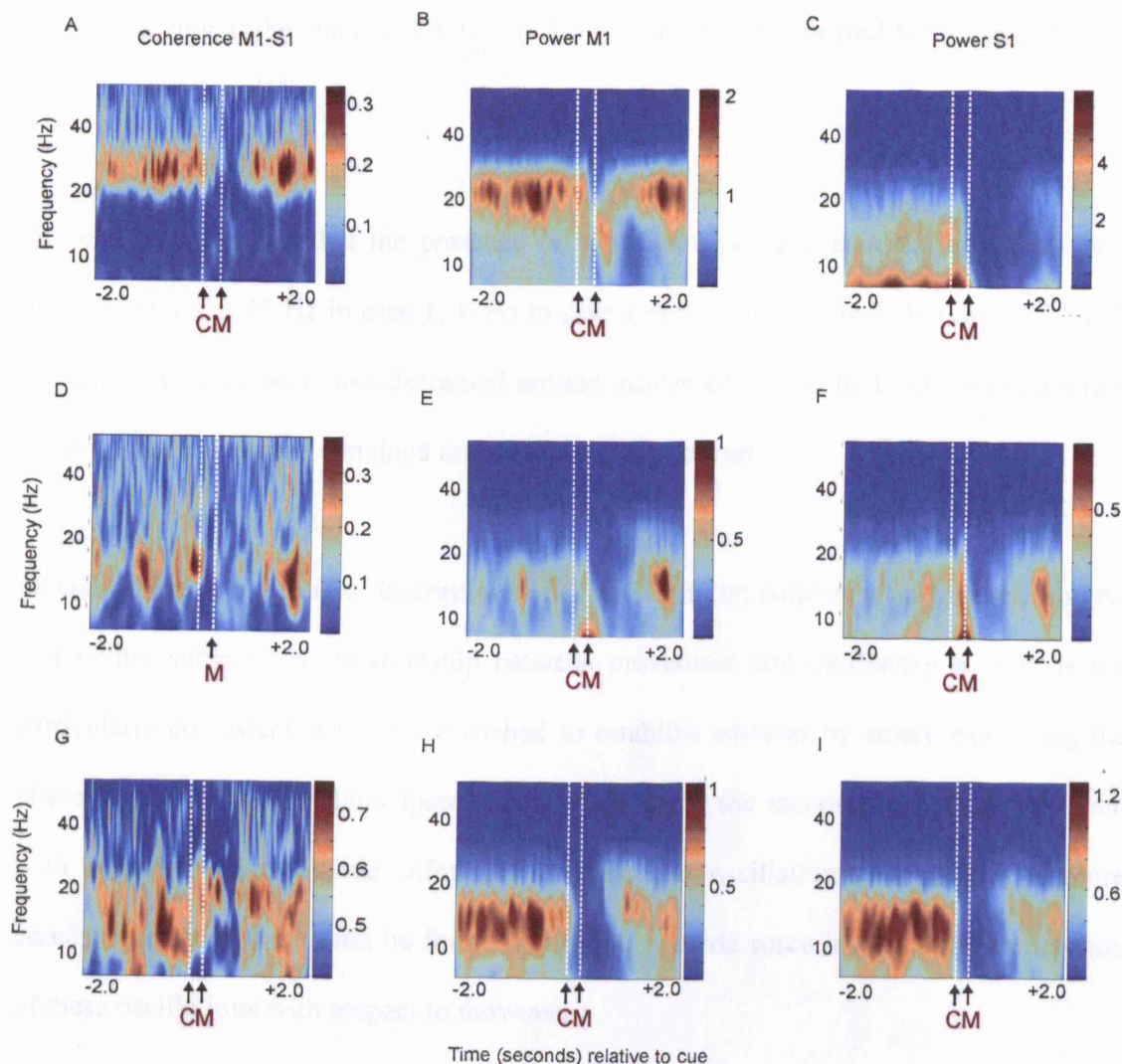
### *Analysis*

Two sets of analysis were performed on these recordings. Firstly I wished to confirm that the event related desynchronisation observed in previous scalp and EcoG recordings could be reproduced in this paradigm and with the electrode positions in these patients. This was achieved by deriving estimates of wavelet power and coherence from the bipolar contacts over M1 (23) and S1 (01) over a time period 2 seconds before and after cue presentation. Analysis was confined to frequencies between 9 and 65 Hz were studied with a frequency resolution of 2Hz.

Time-frequency analysis of the phase concentration during a 1 second period centered around the cue to move was performed using the Raleigh statistic as described in chapter 3. Frequencies between 12 and 48 Hz were analyzed this since frequencies below this level were consistently dominated by the low frequency movement evoked potential.

### **5.1.3. Results**

The time-frequency plots of wavelet power and coherence are plotted for each case in figure 5.1.1. The reaction times for the movement were  $275 \pm 57$  ms ( $n=153$ ),  $263 \pm 88$  ms ( $n=133$ ) and  $240 \pm 55$  ( $n=94$ ) for each case respectively. Prior to cue presentation, time evolving power spectra revealed prominent features centered at  $\sim 21$ Hz in case 1 and at 15Hz in both cases 2 and 3 in M1 and at  $\sim 15$ Hz in all patients over S1; in case 1, an additional 8Hz peak over S1 was also seen. The most common feature seen across the patients was that at the execution of the movement, the power in the beta band was reduced in both the motor and sensory cortices. In the preparatory interval between the cue and the movement a more variable relationship was seen. No obvious suppression of the oscillatory power was seen in case 2 whereas this was a some suppression in cases 1 and 3 in both M1 and S1 at the onset of movement.



**Figure 5.1.1. Event related power and coherence analysis of ECOG**

recorded from M1 and S1 during a cued reaction time task. Each patient's coherence and power for the ECOG in M1 and S1 forms a single row of time-frequency plots with case 1 represented in the first. Note the coherence between M1 and S1 in all patients in the beta band, which suppresses in the first two cases around movement (A and D) and after movement in the third (G). The dynamics of the power changes in both S1 and M1 are similarly inconsistent between subjects with desynchronisation

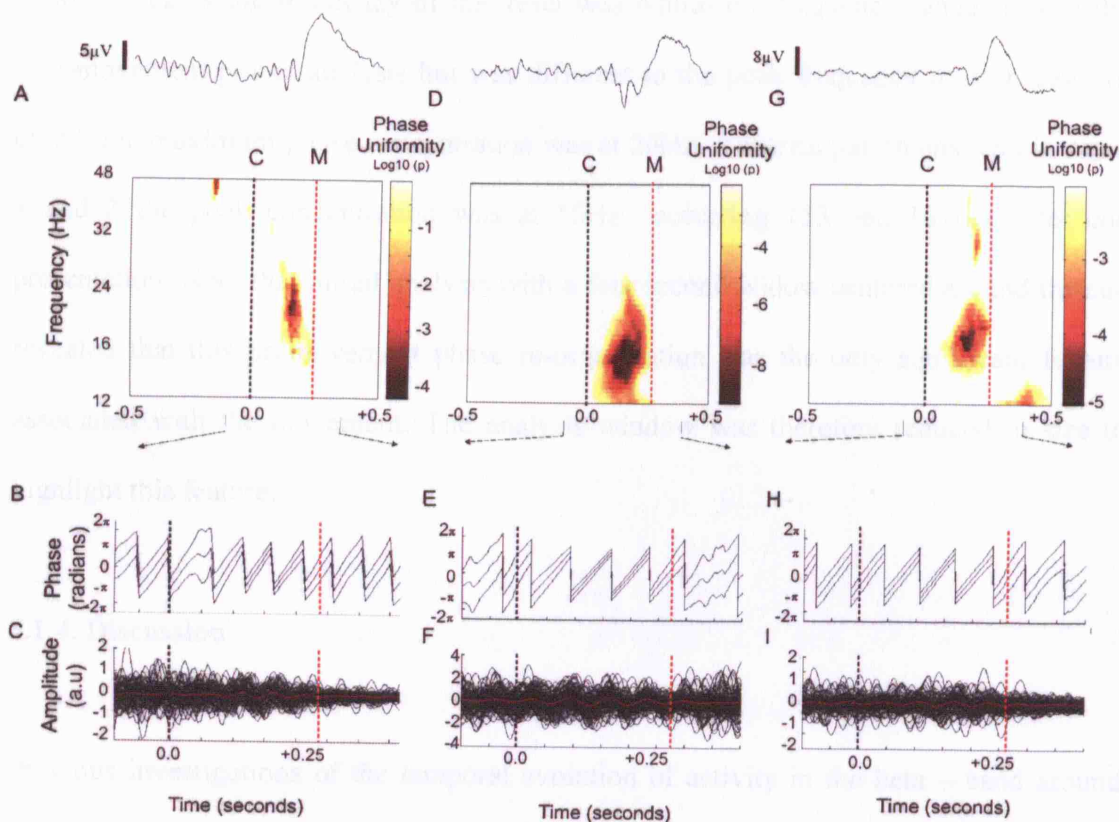
occurring at the cue (red C) in case 3 but at the movement (red M) in cases 1 and 2.

Wavelet analysis revealed the presence of significant coherence in the beta frequency band, centered at 25 Hz in case 1, 17Hz in case 2 and 15Hz in case 3 (Figure 5.1.1, A, D and G). This coherence also decreased around movement in the first two cases, whereas in case 3 the coherence remained throughout the movement.

Overall, these two different descriptions of ECOG activity; coherence and power, suggest that within subjects the relationship between movement and oscillatory activity is not particularly consistent. I therefore wished to establish whether by solely examining the phase of the oscillation, (and therefore by eliminating the inconsistencies that are seen with measures that include information about the oscillation's amplitude) a more consistent relationship could be found that might provide some insight into the function of these oscillations with respect to movement.

In the preliminary analysis phase concentration was analyzed with respect to the onset of the movement, since its reafferent information was hypothesized as an endogenous source of resetting input. However, no significant bins of phase uniformity were detected when the movement onset was used to analyze either the M1 or S1 ECOG in this way. As an alternative frame of reference, I chose the cue onset to apply the phase concentration analysis. The results of this are presented in figure 5.1.2. Significant phase concentration in the M1-LPF was observed in all three patients consistently within the interval between

the cue to move and the movements onset. This prominent resetting was only seen in the M1 ECOG. When the S1-ECOG was analysed short epochs of phase resetting was seen in case 3 but these did not occur for continuous epochs  $> 1$  period of the oscillation at the frequency analyzed. In cases 1 and 2 no time bins with  $p < 0.01$  at beta frequencies were observed.



**Figure 5.1.2. Properties of ECG oscillation phase during a simple reaction time task.** Time frequency plots of the phase uniformity analyses with respect to the cue onset (black dashed line). The raw averaged field potential is plotted above each time-frequency plot. The average reaction time is represented by the red dashed line. Note the phase concentration that

occurs in the beta band between the cue and movement initiation in all three patients (A, D and G). The mean phase  $\pm \log_{10}$  (circular dispersion) is plotted for the wavelet scale which produced the maximal concentration in each subject (B, E and H); the average amplitude (red) and the superimposed single trials are plotted at this scale in C, F and I.

In all the cases the frequency of this reset was within the frequency range seen in the peri-movement power analysis but was different to the peak frequency in each case. In case 3 the maximum phase concentration was at 20Hz ,occurring at 165ms, and in cases 1 and 2 the peak concentration was at 16Hz occurring 153 and 161ms, after cue presentation. Note that initial analysis with a four second widow centered around the cue revealed that this premovement phase re-organization was the only significant feature associated with the movement. The analysis window was therefore reduced in size to highlight this feature.

#### **5.1.4. Discussion**

Previous investigations of the temporal evolution of activity in the beta – band around and during movement have been concerned principally with the description of the power (and amplitude) desynchronisation that occurs around movement. The analysis presented in these studies is limited in that they rely upon averaging the neural activity for their interpretation. The brain clearly cannot have such a luxury, therefore the way in which the oscillation behaves on a single trial is much more representative of the function of the

oscillation than its average representation. Here I have described a consistent organization of oscillatory phase across single trials during the preparatory period of a visually cued finger movement

The most likely pathway for the visual stimuli to access the motor cortical oscillation would be via the lateral premotor cortex (Passingham, 1993). The potential for jitter to accumulate within such a complex pathway may account for the relatively small degree of phase concentration seen in these recordings. In theory, a signal from premotor cortex may be equally capable of resetting the phase of the oscillation, presumably the onset of the visual cue is related to the timing of this signal, but provides only a crude temporal reference once the total jitter within the pathway to M1 accumulates. Therefore the statistically less robust nature of the resetting seen here should not undermine the potential behavioral relevance of this observation.

The time course of the phase resetting here would coincide with the changes in firing rates in M1 neurons associated with the preparation for movement. However, the cue rather than the movement was the driving stimulus for phase alignment. This would argue that this response to the cue is more likely to be involved in its sensory representation within M1 than the organization of motor output, at least not directly. Relevant to this discussion is the observations of O'Leary and Hatsopoulos (2006) who observed a similar phase reset in monkey dorsal premotor cortex and M1 during a choice reaction time task. Interestingly, LFP at beta frequencies could be used to decode the direction of the cue on

a single trial basis. These results may support the notion that the phase reset seen here, performs some role in the representation of input into the motor cortex about the timing, and potentially other features of sensory stimulus.

From a biophysical point of view, a predictable oscillating state may be better than an unpredictable stochastic membrane noise for the neural coding of sensory input. If oscillations are involved in the improvement of spike timing reliability then by simply generating an oscillation without any respect to its phase should improve coding. The role of the reset in this context therefore must be to align the coding of the movement to a specific part of the oscillation's cycle. This implies therefore, that the oscillation's membrane potential is not symmetrically beneficial for improving the reliability of rate coding functions. Recently Schaeffer et. al. (2006) have demonstrated *in vitro* that the hyperpolarizing phase of a membrane potential oscillation removes the accumulative error in action potential timing, (that accumulates over time during tonic action potential firing). The phase reset observed here could therefore be timed to eliminate the previous firing history of the neuron in an attempt to provide optimal conditions for the subsequent coding of the sensorimotor transformation. Of course, this explanation for the reset assumes that the code for such a sensorimotor transformation is represented in the precise timing of M1 neuron action potentials. Although this has not been proven for M1, it is interesting to note that the inter-trial variability of spike timing in the premotor cortex decreases immediately prior to movement (Churchman, 2006).





## **Chapter 6: Final Discussion and Overview of the thesis**

The principal findings of this thesis are as follows:-

1. Rhythmic 13-30 Hz neural oscillations in the corticospinal tract are associated with impaired transitions from postural to ballistic motor sets in healthy humans.
2. This oscillatory activity is associated with enhanced cortical responses to afferent input from peripheral sensory receptors.

I will discuss some general implications and future predictions that these results may provide in the context of physiological motor control.

### **6.1 Slowed movements and corticospinal beta oscillations**

What is the significance of this thesis in the context of understanding the mechanisms that contribute to bradykinesia in Parkinson's disease? One key issue in the interpretation of the data in this context is that whatever detrimental effect beta oscillations might have on movement, it must be a universal property of these oscillations across multiple different neuronal populations. The main reason for arguing that a generic property of these oscillations must produce bradykinesia in PD rather than corticospinal muscle

oscillations in the beta band is that these are simply not present in the bradykinetic parkinsonian state (Salenius et. al., 2001). In this regard, if beta oscillations projected to muscle from cortex produce slowed finger movements by affecting spinal motoneuron recruitment, this clearly cannot be seen as a mechanism for bradykinesia in Parkinson's disease. The cortical correlate of this effect observed in the EcoG recordings would argue that corticospinal neurons may be affected in a similar way; however, it is impossible from these data to state specifically whether the slowed movements are the manifestation of impaired cortical or spinal processing – the most likely explanation is that both are affected by the same process. Beta bursts in the microtremor may therefore be viewed as an index of oscillatory activity that may provide accessible insights into the effects of these oscillations on neuronal processing, but not a stand alone explanation for bradykinesia in Parkinson's disease in its own right.

What sort of generic neuronal processing effect might these oscillations, irrespective of there site, cortical, spinal, or otherwise, induce to result in the slowing of ballistic movements? One possibility alluded to in the other discussion chapters was an effect mediated by some sort of short term plastic process. This is an immediately attractive thought since it easily reconciles the delay between the triggering oscillation and the onset of movement, by arguing for some sort of short term synaptic change in efficacy at cortico-motoneuronal or even intracortical synapses. Indeed, some *in vitro* studies have postulated a role for beta oscillations in synaptic plasticity and memory (Traub et. al., 1999; Bibbig et. al., 2002), although direct evidence for oscillation induced plasticity in the intact motor system is lacking. The problem with this explanation, although it is

difficult to disprove that such a process might be implicated, is that it is equally difficult to prove (certainly in the awake behaving human or monkey) that these oscillations are somehow implicated in short term regulation of synaptic gain. Nevertheless, a role in plasticity remains an important issue for future investigations.

What other properties common to both lower motoneurons and corticospinal tract neurons might reconcile the beta oscillation “after effects”? An interesting candidate mechanism would be spike frequency adaptation (SFA). This property is characterised by the progressive increase in the ISI of neurons to either a noisy or constant current synaptic input (typically occurring within 0.5-1 seconds). SFA has been observed in pyramidal neurons of layer V sensorimotor neurons in the cat (Schwindt et. al., 1988; Stafstrom et. al., 1984), in human neocortical pyramidal neurons (Avoli and Olivier, 1989; Lorenzon and Foehring, 1992) and classically in rat motoneurons (Granit et. al., 1963; Kernell, 1965; Sawczuk et. al, 1995, 1997, Kernell and Monster, 1982). The effect of SFA is essentially to make the neuron considerably less reactive to depolarizing input. SFA is biophysically indexed by a progressive increase in the depth and size of the After-Hyperpolarisation Potential (AHP), (Maddison and Nicoll, 1984; Schwindt et, al., 1988). Indeed, this process has been previously suggested as the mechanism for the reduction of slowed ballistic movements when these are made from a background level of tonic contraction (Van Cutsem and Duchateau, 2005). In the reaction time experiments of chapter 3 the movements were all made from a background level of contraction, therefore if SFA contributes to the slowing of these movements, then the oscillations may produce SFA over and above that expected by a desynchronized (non-oscillatory) tonic

contraction. It is interesting to note therefore that *in vitro* studies of oscillatory activity in neocortical networks, SFA has been proposed as a crucial factor in determining the frequency of oscillatory activity across populations of neurons (Fuhrmann et. al., 2002). Therefore the beta oscillations used to trigger the cue in the experiments of chapter 3 may reflect synchronised cortical and motoneuronal populations which are undergoing or have undergone adaptation. This would leave these neurons in a less reactive state to the input required for producing effective ballistic contraction. Importantly to any theory that might explain this after effect, the motoneuron or cortical neuron will retain this reduced reactivity until it is repolarised and its firing history can be erased (Powers et. al., 2005). Therefore the oscillation could index SFA across a large number of neurons 350ms before the movement and the effects of this process could outlive the oscillation itself.

An important further property of SFA is that it may be produced by membrane potential that is below threshold for action potential firing (Kernell, 1999; Alaburda et. al., 2002). This is critical for a SFA mediated mechanism here, since it would be the effect of cross talk, between the suprathreshold motoneurons engaged in the tonic postural contraction and the higher threshold motoneurons, (required for the ballistic force at contraction onset), that would produce the slowing observed in these experiments. A final point to emphasise here, in the context of this idea, is that the SFA would not reduce the excitability of the supraspinal or spinal motoneuron pool. It would specifically impair the ability to recruit a rapid change in motoneuron firing rates required for ballistic movement. An explanation involving SFA would not therefore be incompatible with the increased cortical reflex response to muscle stretch, assuming that the stretch itself does

not require rapid increases in firing rate over and above normal levels of motor unit recruitment. Indeed in contrast to the specific recruitment order of high threshold units in ballistic movements, reflexive responses to stretch do not show any simple recruitment profile (Calancie and Bawa, 1985).

In previous chapters I argued that the early onset of the beta oscillation-peak acceleration correlations may be the consequence of an interaction with mechanisms that are involved in the preparation for movement rather than the execution. An alternative hypothesis which would be more consistent with this idea is that the oscillation, rather than being associated with enhanced SFA, is somehow an impairment to any process(es) that attempt to erase the past firing history of SFA within the lower motoneuron pool. Any putative mechanism that might perform such a function must be able to repolarise the motoneuron membrane since it is this process that resets the AHP length (Erisir et. al., 1999). There are two possible processes described previously that would occur in the premovement period at a time consistent with an attempt to perform such a function. Firstly, the silent period (typically 80ms prior to EMG onset) has been known to correlate well with the force produced during a ballistic movement (Tsukahara et. al., 1995; Yabe, 1976; Mortimer et. al., 1987; Conrad et. al., 1983). Furthermore, this is thought to be produced by corticospinal fibres since the silent period is associated with reduced MEP but not H-reflex responses (Aoki et. al., 2002) and STA from identified pyramidal tract neurons often reveal an inhibitory descending drive to spinal motoneurons (Lemon et. al., 1986; Weidner and Cheney, 1997). Secondly, the presynaptic inhibition of afferent (cutaneous) input may also be critical for generating ballistic force since these afferents

inhibit EMG activity (Aeki et. al., 2004; Jenner and Stephens, 1982) and increase the threshold for motor unit recruitment (Stephens et. al., 1979). Whether either of these processes actively eliminates the affect of motoneuron firing history is a matter of speculation (Van Cutsem and Duchateau, 2005). Nevertheless, the phase resetting seen in the EcoG recordings presented in chapter 5 would be more likely to coincide with these processes than the firing rate increase associated with movement onset. If the beta phase resetting were somehow involved in the organization of presynaptic inhibition (Andersen et. al., 1962) and corticospinal inhibition of the motoneuron pool prior to movement, then the negative relationship between PA and beta amplitude around the time of cue presentation may reflect a simple inability of the beta oscillation to be reset when the amplitude is large. Therefore the effect of large oscillations at the time of cue presentation would be to prevent resetting of the phase of the oscillation, and therefore produce an in appropriately timed descending cortical facilitation of spinal inhibitory drive, which would not be optimally coupled to the subsequent excitatory volley that drives the motoneurons to threshold. This framework would be consistent with the observation that the premovement silent period in PD is unaffected in terms of its duration or incidence, but does not provide any benefit to the speed of the movement. In other words the EMG silence prior to movement in PD is uncoupled with the descending drive that initiates the movement (Palmer et. al, 1991).

## 6.2 Final remarks

The aim of the experiments presented in this thesis was to characterise further the physiological properties of corticospinal oscillations in the beta (13-30Hz) range, with specific reference to models of parkinsonian symptomology. In this final discussion I have emphasised the likelihood that the basic properties of neurons engaged in beta frequency activity can probably be generalised across the different brain regions in which this activity is seen. It should be noted however, that understanding the effects of corticospinal beta oscillations on movement specifically, over and above elucidating generalised principles, may be critical to future plans for cortical stimulation in these patients (Drouot et. al., 2004). The therapeutic effects of this neurosurgical option, which, in theory has considerable advantages over conventional DBS has been reported to be variable (Kleiner-Fisman, et. al., 2003). Testing some of the hypothetical mechanisms for bradykinesia described above may provide a better understanding of this symptom and a more robust rationale for this type of treatment.



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## Appendix

The following publications were derived from work included in this thesis:

Gilbertson, T. Lalo, E. . Doyle, L. Di Lazzaro, V. Cioni, B. Brown, P. Existing motor state is favored at the expense of new movement during 13-35 Hz oscillatory synchrony in the human corticospinal system. (2005) J Neurosci 25(34):7771-9.

Lalo, E. Gilbertson, T. Doyle, L. Di Lazzaro, V. Cioni, B. Brown, P. (2006) Phasic increases in cortical beta activity are associated with alterations in sensory processing in the human. Exp Brain Res. In press.

Androulidakis AG, Doyle LMF, Gilbertson TP, Brown P. (2006) Eur J Neurosci, Submitted. Corrective movements in response to displacements in visual feedback are more effective during periods of 13-35 Hz Oscillatory Synchrony in the Human Corticospinal system.